

TOXICOLOGICAL PROFILE FOR
AMMONIA

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

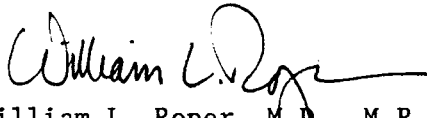
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about ammonia and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1177 sites on its National Priorities List (NPL). Ammonia has been found at 23 of these sites. However, we do not know how many of the 1177 NPL sites have been evaluated for ammonia. As EPA evaluates more sites, the number of sites at which ammonia is found may change. The information is important for you because ammonia may cause harmful health effects and because these sites are potential or actual sources of human exposure to ammonia.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as ammonia, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS AMMONIA?

Ammonia is a chemical made by both man and nature. The amount of ammonia produced every year by man is very small compared to that produced by nature every year. However, when ammonia is found at a level that may cause concern, it is usually produced either directly or indirectly by man. Ammonia is a colorless gas with a very sharp odor. The odor is familiar to most people because ammonia is used in smelling salts, household cleaners, and window cleaning products. Ammonia easily dissolves in water. In water, most of the ammonia changes to ammonium, which is not a gas and does not smell. Ammonia and ammonium can change back and forth in water. In wells, rivers, lakes, and wet soils, the ammonium form is most common.

Ammonia is very important to animal and human life. It is found in water, soil, and air, and is a source of much-needed nitrogen for plants and animals. Most of the ammonia in the environment comes from the natural breakdown of manure and dead plants and animals.

Eighty percent of all man-made ammonia is used as fertilizer. A third of this is applied directly as pure ammonia. The rest is used to make

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other fertilizers that contain ammonium. Ammonia is also used to manufacture synthetic fibers, plastics, and explosives. Many cleaning products also contain ammonia.

Ammonia does not last very long in the environment. Because it is recycled naturally, nature has many ways of incorporating and transforming ammonia. In soil or water, plants and microorganisms rapidly take up ammonia. After fertilizer containing ammonia is applied to soil, the amount of ammonia in that soil decreases to low levels in a few days. In the air, ammonia will last about one week.

In the air near hazardous waste sites, ammonia can be found as a gas. Ammonia can be found dissolved in ponds or other bodies of water at a waste site. Ammonia can also be found sticking to soil at hazardous waste sites. The average concentration of ammonia reported at hazardous waste sites ranges from 1 to 1000 parts of ammonia to one million parts of soil (ppm) in soil and up to 16 ppm in water samples.

For detailed information on the chemical properties of ammonia, see Chapter 3. Details on the production and use of ammonia are in Chapter 4, and more information on the environmental fate of ammonia and sources of human exposure are in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO AMMONIA?

Since ammonia occurs naturally in the environment, we are regularly exposed to low levels of ammonia in air, soil, and water. Ammonia has been found in both soil and water samples at hazardous waste sites. Ammonia exists naturally in the air at levels between one part and five parts in a billion parts of air (ppb). It is commonly found in rain water. The ammonia levels in rivers and bays are usually less than 6 ppm (6 ppm = 6,000 ppb). Soil typically contains about 1 to 5 ppm of ammonia. The levels of ammonia vary throughout the day, as well as from season to season. Generally, ammonia levels are highest in the summer and spring, when nature is most active.

Outdoors, you may be exposed to high levels of ammonia in air from leaks and spills at production plants and storage facilities, and from pipelines, tank trucks, rail cars, ships, and barges that transport ammonia. Higher levels of ammonia in air may occur when fertilizer is applied to farm fields. After fertilizer is applied, the concentration of ammonia in soil can be more than 3000 ppm; however, these levels decrease rapidly over a few days. Indoors, you may be exposed to ammonia while using household products that contain ammonia. Some of these products are ammonia cleaning solutions, window cleaners, floor waxes, and smelling salts.

You can also be exposed to ammonia at work because many of the cleaning products there also contain ammonia. Farmers, cattle ranchers, and

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people who raise chickens can be exposed to ammonia from decaying manure. Some manufacturing processes also use ammonia.

See Chapter 5 for more detailed information on the environmental fate of ammonia, ammonia levels in the environment, and exposure to ammonia.

1.3 HOW CAN AMMONIA ENTER AND LEAVE MY BODY?

Ammonia can enter your body if you breathe in ammonia gas or if you swallow water or food containing ammonia. If you spill ammonia on your skin, a small amount of ammonia might enter your body through your skin; however, more ammonia will probably enter as you breathe the fumes from the spilled ammonia. After you breathe in ammonia, you breathe most of it out again. If you swallow ammonia in food or water, it will get into your bloodstream and be carried throughout your body within minutes. Most of the ammonia that enters your body rapidly changes into other substances that will not harm you. The rest of this ammonia leaves your body in urine within a couple of days. For more information on how ammonia can enter and leave your body, see Chapter 2.

1.4 HOW CAN AMMONIA AFFECT MY HEALTH?

If you were exposed to much higher than normal amounts, you would experience some effects. For example, if you spilled a bottle of concentrated ammonia on the floor, you would smell a strong ammonia odor; you might cough, and your eyes might water because of irritation. If you were exposed to very high levels of ammonia, you would experience more harmful effects. For example, if you walked into a dense cloud of ammonia or spill concentrated ammonia on your skin, you might get severe burns on your skin, eyes, throat, or lungs. These burns might be serious enough to cause permanent blindness, lung disease, or death. Likewise, if you accidentally ate or drank large amounts of ammonia, you might experience burns in your mouth, throat, and stomach. Based on available data, we cannot say with certainty whether or not ammonia causes cancer or birth defects. Ammonia can also have beneficial effects, such as when it is used as a smelling salt. Certain ammonium salts have long been used in veterinary and human medicine. For more information on how ammonia can affect your health, see Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The levels of ammonia in air, drinking water, and food that affect your health are summarized in Tables 1-1 through 1-4. Ammonia has a very strong odor that you can smell when it is in the air at a level higher than 50 ppm. Therefore, you will probably smell ammonia before you are exposed to a concentration that may harm you. As seen in Table 1-2, levels of ammonia in air that cause serious effects in animals are much higher than levels you would normally be exposed to at home or work.

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TABLE 1-1. Human Health Effects from Breathing Ammonia*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects**</u>
0.5		Minimal Risk Level (see Section 1.5 for discussion).
50	less than 1 day	Slight, temporary eye and throat irritation and urge to cough.
500	30 minutes	Increased air intake into lungs; sore nose and throat.
5000	less than 30 minutes	Kills quickly.
Long-term Exposure (greater than 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects**</u>
0.3		Minimal Risk Level (see Section 1.5 for discussion).
100	6 weeks	Eyes, nose and throat irritation.

*See Section 1.2 for a discussion of exposures encountered in daily life.

**These effects are listed at the lowest level at which they were first observed. They may also be seen at the higher levels.

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TABLE 1-2. Animal Health Effects from Breathing Ammonia

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
50	3 hours	Slowed breathing rate in rabbits; coughing, eye, mouth, and nose irritation, poor weight gain and food intake in pigs.
100	6 hours	Increased irritability in rats.
500	7 days	Decreased weight gain and food intake in rats. Decreased resistance to disease in mice.
1000	16 hours	Death in rats and mice.
Long-term Exposure (greater than 14 days)		
<u>Levels in Air (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
653	90 days	Death in rats.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

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TABLE 1-3. Human Health Effects from Eating or Drinking Ammonia*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u> The health effects resulting from short-term human exposure to food containing specific levels of ammonia are not known.
<u>Levels in Water</u>		The health effects resulting from short-term human exposure to water containing specific levels of ammonia are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects**</u> The health effects resulting from long-term human exposure to food containing specific levels of ammonia are not known.
<u>Levels in Water (ppm)</u> 10		Minimal risk level (based on animal studies; see Section 1.5 for discussion.

*See Section 1.2 for a discussion of exposures encountered in daily life.

**These effects are listed at the lowest level at which they were first observed. They may also be seen at the higher levels.

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TABLE 1-4 Animal Health Effects from Eating or Drinking Ammonia

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
		The health effects resulting from short-term animal exposure to food containing specific levels of ammonia are not known.
<u>Levels in Water (ppm)</u>		
1192	1 day	Death; swelling and blocking of lung passages in guinea pigs.
3093	7 days	Enlarged kidney in rats.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
		The health effects resulting from long-term animal exposure to food containing specific levels of ammonia are not known.
<u>Levels in Water (ppm)</u>		
564	90 days	Reduced food intake and poor weight gain in rats.
1127	17 months	High blood pressure and enlarged adrenal glands in rabbits.
7027	11 weeks	Bone deformity and softening in dogs.
21,609	36 days	Swelling and infection in kidneys of rabbits.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

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You can taste ammonia in water at levels of about 35 ppm. Lower levels than this occur naturally in food and water. Swallowing even small amounts of ammonia in your household cleaner might cause burns in your mouth and throat. A few drops of liquid ammonia on the skin or in the eyes will cause burns and open sores if not washed away quickly. Exposure to larger amounts of ammonia in the eyes causes severe eye burns and can lead to blindness. Minimal Risk Levels (MRLs) are also included in Tables 1-1 and 1-3. These MRLs were derived from human and animal data for short-term and long-term exposure, as described in Chapter 2 and in Tables 2-1 and 2-2. The MRLs provide a basis for comparison with levels that people might encounter either in the air or in food or drinking water. If a person is exposed to ammonia at an amount below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because these levels are based only on information currently available, some uncertainty is always associated with them. Also, because the method for deriving MRLs does not use any information about cancer, an MRL does not imply anything about the presence, absence, or level of risk for cancer.

For more information on levels of exposure associated with effects, see Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO AMMONIA?

There are tests that measure ammonia in blood and urine; however, these tests would probably not tell you whether you have been exposed because ammonia is normally found in the body. If you were exposed to harmful amounts of ammonia, you would notice it immediately because of the strong unpleasant smell, the strong taste, and the skin, eye, nose, and throat irritation. This is discussed in greater detail in Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The Environmental Protection Agency (EPA) regulates the ammonia content in wastewater released by several industries. Any discharges or spills of ammonia of 100 pounds or more, or of ammonium salts of 1000 or 5000 pounds (depending upon the compound) must be reported to EPA.

Some restrictions have been placed on levels of ammonium salts allowable in processed foods. The U.S. FDA (1973) determined that the levels of ammonia and compounds normally found in food do not pose a health risk; ammonia is necessary for normal functions. Maximum allowable levels in processed foods are as follows: 0.04 to 3.2% ammonium bicarbonate in baked goods, grain, snack foods, and reconstituted vegetables; 2.0% ammonium carbonate in baked goods, gelatins, and puddings; 0.001% ammonium chloride in baked goods and 0.8% in condiments and relishes; 0.6-0.8% ammonium hydroxide in baked goods, cheeses, gelatins, and puddings; 0.01% monobasic

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ammonium phosphate in baked goods; 1.1% dibasic ammonium phosphate in baked goods, 0.003% in nonalcoholic beverages, and 0.012% for condiments and relishes.

The Occupational Safety and Health Administration (OSHA) has set a short-term (15 minute) exposure limit of 35 ppm for ammonia. The National Institute for Occupational Safety and Health (NIOSH) recommends that the level in workroom air be limited to 50 ppm for 5 minutes of exposure. Further information on governmental recommendations can be found in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This Chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to ammonia. Its purpose is to present levels of significant exposure for ammonia based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of ammonia and (2) a depiction of significant exposure levels associated with various adverse health effects.

A prerequisite to understanding the potential health hazards associated with environmental exposure to ammonia is an appreciation of ammonia as both a potentially toxic agent and an essential chemical for humans. Ammonia is produced in the human body from metabolism of protein, amino acids, and other nitrogen-containing chemicals. This endogenous ammonia serves an important role in nitrogen metabolism and in the maintenance of acid/base balance. A large amount of ammonia (≥ 50 mg/kg) is produced in the body each day as a result of the breakdown of dietary protein and amino acids.

The considerable rate of endogenous ammonia production is important to consider when evaluating the potential health effects of short or longterm exposure to exogenous sources of ammonia.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and graphs may differ depending on the user's perspective. For example, physicians

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concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed.

Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike. Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

In the discussion of effects of ammonia by route of exposure, it is necessary to consider ammonium compounds for oral exposure because oral studies in animals generally involve exposure to ammonium salts or ammonium hydroxide. Inhalation exposure involves exposure to ammonia gas. Although inhalation exposure to aerosols of ammonium compounds is conceivable, no studies were located regarding inhalation exposure of humans or animals to other forms of ammonia.

2.2.1 Inhalation Exposure

2.2.1.1 Death

There are many reports in the literature of human deaths resulting from inhalation of ammonia (Burns et al. 1985; Close et al. 1980; Couturier et al. 1971; Heifer 1971; Price et al. 1983; Sobonya 1977; Yang et al. 1987). Most of these reports are of acute accidental exposure to concentrated aerosols of anhydrous ammonia. A review of the early literature on ammonia toxicity cites short-term exposure to 5000-10,000 ppm as being rapidly fatal in humans (Henderson and Haggard 1927, Mulder and Van der Zalm 1967). Immediate deaths resulting from acute exposure to ammonia appear to be caused by airway obstruction while infections and other secondary complications are lethal factors among those who survive for several days or weeks. Chemical burns and edema of exposed tissues, including the respiratory tract, eyes and exposed skin, are often observed

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after exposure to lethal levels. No reports of human death due to intermediate or chronic exposure to ammonia were located.

As shown in Table 2-1, studies in animals indicate that the acutely lethal exposure concentration depends on the exposure duration. The lethal concentration in rats and mice increases 5-10 times as the exposure duration decreases from 16 hours to several minutes (Hilado et al. 1977; Kapeghian et al. 1982; Prokop'eva et al. 1973; Weedon et al. 1940). Exposure frequency also appears to be an important factor in determining lethality. Continuous exposure to 653 ppm for 25 days resulted in nearly 64% lethality in rats, whereas intermittent exposure to nearly twice this concentration was tolerated for 42 days (Coon et al. 1970). It appears that male rats are more sensitive than female rats to the lethal effects of ammonia (Appelman et al. 1982; Stupfel et al. 1971). Animals exposed to acutely lethal concentrations show severe lesions in the respiratory tract that are similar to those observed in humans. Less severe lesions of the liver, heart, and kidney have been observed following continuous long-term exposure to lethal concentrations (Coon et al. 1970). However, these probably represent secondary complications from chronic respiratory tract injury.

2.2.1.2 Systemic Effects

Respiratory Effects. Ammonia is an upper respiratory irritant in humans. Exposures to levels exceeding 50 ppm result in immediate irritation to the nose and throat; however, tolerance appears to develop with repeated exposure (Verberk 1977). Thus, subjects exposed to 100 ppm for 6 weeks experienced nose and throat irritation only during the first week (Ferguson et al. 1977). Acute exposure to higher levels (500 ppm) have been shown to increase respiratory minute volume (Silverman et al. 1949). Buff and Koller (1974) suggest that this is due to an effect on "irritant receptors" in the lungs resulting in increased activity of reflex respiratory muscles. Accidental exposures to concentrated aerosols of anhydrous ammonia or high concentrations of ammonia gas have resulted in nasopharyngeal and tracheal burns, airway obstruction and respiratory distress, and bronchiolar and alveolar edema (Burns et al. 1985; Close et al. 1980; Couturier et al. 1971; Hatton et al. 1979; Heifer 1971; Price et al. 1983; Sobonya 1977; Taplin et al. 1976). Chronic occupational exposure (about 14 years) to low levels of airborne ammonia (12.5 ppm) had no effect on pulmonary function or odor sensitivity in a group of workers at a soda ash factory compared to a control group from the same factory that was not exposed to ammonia (Holness et al. 1989). An acute inhalation MRL of 0.5 ppm was derived from the Verberk (1977) study, and a chronic inhalation MEL of 0.3 ppm was derived from the Holness et al. (1989) study; MRLs are presented in Table 2-1 and Figure 2-1.

Studies in animals have demonstrated similar dose-effect and duration effect patterns for the respiratory tract. Acute exposures to low concentrations of ammonia (≤ 1000 ppm) irritate the upper respiratory tract whereas exposures to high concentrations (≥ 4000 ppm) result in severe damage

TABLE 2-1. Levels of Significant Exposure to Ammonia - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Death							
1	Human	1 d 30 min/d				5000 ^a (Rapidly fatal)	Henderson and Haggard 1927
2	Rat	1 d 16 hr/d				1000 ^b (LC ₅₀)	Weedon et al. 1940
3	Rat	1 d 15 min/d				17,401 (LC ₅₀)	Prokop'eva et al 1973
4	Mouse	1 d 16 hr/d				1000 ^b (LC ₅₀)	Weedon et al. 1940
5	Mouse	1 d 30 min/d				21,430 (LC ₅₀)	Hilado et al. 1977
6	Mouse	1 d 60 min/d				11,299 (LC ₅₀)	Prokop'eva et al 1973
7	Mouse	1 d 1 hr/d				4230 (LC ₅₀)	Kapeghian et al. 1982
8	Rabbit	1 d 1 hr/d				10,050 (LC ₅₀)	Boyd et al. 1944
9	Cat	1 d 1 hr/d				10,050 (LC ₅₀)	Boyd et al. 1944
Systemic							
10	Human	1 d 30 min/d	Resp		500 ^a (Nasal and throat irritation; increased minute volume)		Silverman et al. 1949
			Cardio	500			

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
Systemic							
11	Human	1 d 2 hr/d	Resp		50 ^{a,c} (Urge to cough, irritation to nose throat)		Verberk 1977
			Derm/oc		50 ^a (Irritation to eyes)		
12	Rat	1 wk 24 hr/d	Resp		500 (Irritation)		Richard et al. 1978a
			Renal	500			
			Other		500 ^b (Decreased bw and food intake)		
13	Rat	7 d	Resp		714 (mild epithelial damage)		Schaerdel et al. 1983
			Renal	714			
			Derm/oc	714			
			Other	714			
14	Mouse	1 hr	Resp			4070 (Alveolar destruction)	Kapeghian et al. 1982
			Cardio			4070 (Atrophy of pericardial fat)	
			Hemato			4070 (Intra-alveolar hemorrhage, vascular congestion)	
			Hepatic			4070 (Increased weight, necrosis)	
15	Rabbit	1 d 3 hr/d	Resp		50 ^b (Decreased respiratory rate, respiratory depth increased)		Mayan and Merilan 1972
			Hepatic	100			
			Renal	100			
16	Rabbit	1 wk 5 d/wk 8 hr/d	Resp	225	1105 (Temporary dyspnea)		Coon et al. 1970
			Derm/oc	155	1105 (Temporary lacrimation)		
17	Rabbit	1 d 60 min/d	Resp			5000 (Acute pulmonary edema)	Richard et al. 1978b
			Cardio		2500 (Bradycardia)	5000 (Hypertension, acidosis, EKG change)	

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
Systemic							
18	Dog	1 wk	Resp 5 d/wk 8 hr/d	155	770	(Temporary dyspnea)	Coon et al. 1970
19	Pig	1 wk	Resp Derm/oc Other		100 50 50	(Excessive nasal secretion, coughing) (tracheal inflammation) (Excessive lacrimation) (Reduced weight gain)	Drummond et al. 1980
20	Pig	1 wk	Hemato Derm/oc	100	100	(Ocular irritation)	Doig and Willoughby 1971
21	Pig	3 d	Resp Derm/oc Other	10 10 10	50 ^b 50 ^b 50 ^b	(Frequent coughing, oral and nasal irritation) (Ocular irritation) (Reduced weight gain, reduced food intake)	Stombaugh et al. 1969
Immunological							
22	Mouse	7 d 24 hr/d			500 ^b	(Decreased resistance to infection)	Richard et al. 1978a
Neurological							
23	Rat	1 d 6 hr/d			100 ^b	(Aversion to sensory irritation)	Tepper et al. 1985
24	Mouse	5 d			500	(Lethargy; altered enzyme activity)	Sadasivudu et al. 1979
25	Mouse	1 d 6 hr/d			100	(Aversion to sensory irritation)	Tepper et al. 1985
26	Pig	4 wk		50	100	(Lethargy)	Drummond et al. 1980

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
Death							
27	Rat	90 d		376		653 ^b (99% death)	Coon et al. 1970
28	Dog	6 wk 5 d/wk 8 hr/d		1105			Coon et al. 1970
Systemic							
29	Human	6 wk 5 d/wk 6 hr/d	Resp	50	100 ^a (Transient irritation of nose and throat)		Ferguson et al. 1977
			Derm/oc	50	100 ^a (Transient eye irritation)		
			Cardio	100			
30	Rat	6 wk 5 d/wk 8 hr/d	Resp	225	1105 (Temporary dyspnea, non-specific inflammation)		Coon et al. 1970
			Cardio	1105			
			Hemato	1105			
			Hepatic	1105			
			Renal	1105			
			Derm/oc		1105 (Temporary lacrimation)		
31	Rat	4 wk 24 hr/d	Resp		150 (Nasal lesions, epithelial hyperplasia)		Broderson et al. 1976
			Cardio		150 (Localized vascular dilatation)		
32	Rat	90 d	Resp	182	376 (Mild nasal discharge in 25% animals)	653 (Interstitial pneumonitis)	Coon et al. 1970
			Cardio	376		653 (Myocardial fibrosis)	
			Hepatic	376	653 (Fatty changes of liver plate cells)		
			Renal	376		653 (Renal tubular calcification)	

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
Systemic							
33	Gn Pig	3 wk	Resp Hemato Other	90 90 90			Targowski et al. 1984
34	Gn Pig	18 wk 5 d/wk 6 hr/d	Resp Cardio Gastro Hemato Hepatic Renal	170 170 170	170 (Increased hemosiderin) 170 (Congestion) 170 (Congestion)		Weatherby 1952
35	Gn Pig	6 wk 5 d/wk 8 hr/d	Resp Hemato Hepatic Renal Derm/oc Cardio	225 1105 1105 1105 1105 1105	1105 (Non-specific inflammation)		Coon et al. 1970
36	Rabbit	114 d	Resp Cardio Hemato Hepatic Renal Derm/oc	57 57 57 57 57 57			Coon et al. 1970
37	Monkey	6 wk 5 hr/wk 8 hr/d	Resp Cardio Hemato Hepatic Renal Derm/oc	1105 1105 1105 1105 1105 1105	225 (Focal pneumonitis)		Coon et al. 1970

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect)		Reference
					Less Serious (ppm)	Serious (ppm)	
Immunological							
38	Rat	4 wk 24 hr/d			25	(Enhanced severity of infection by <u>Mycoplasma</u>)	Richard et al. 1978a
39	Gn Pig	3 wk			90	(Decreased immune response)	Targowski et al. 1984
40	Pig	31-45 d			100	(Increased conc. of gamma globulin)	Neumann et al. 1987
Neurological							
41	Gn Pig	6 wk 5 d/wk 8 hr/d		1105			Coon et al. 1970
42	Monkey	6 wk 5 hr/wk 8 hr/d		1105			Coon et al. 1970
CHRONIC EXPOSURE							
Systemic 43	Human	15 yr 5 d/wk 8 hr/d	Resp Derm/oc	12.5 ^d 12.5			Holness et al. 1989

^aPresented in Table 1-1.^bPresented in Table 1-2.^cUsed to derive acute MRL of 0.5 ppm, which is presented in Table 1-1; concentration divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL).^dUsed to derive chronic inhalation MRL of 0.3 ppm, which is presented in Table 1-1; concentration adjusted for intermittent exposure and divided by an uncertainty factor of 10 for human variability.

bw = body weight; Cardio = cardiovascular; d = day; Derm/oc = dermal/ocular; Hemato = hematological; gastro = gastrointestinal; Gn Pig = guinea pig; hr = hour; min = minute; Resp = respiratory; wk = week.

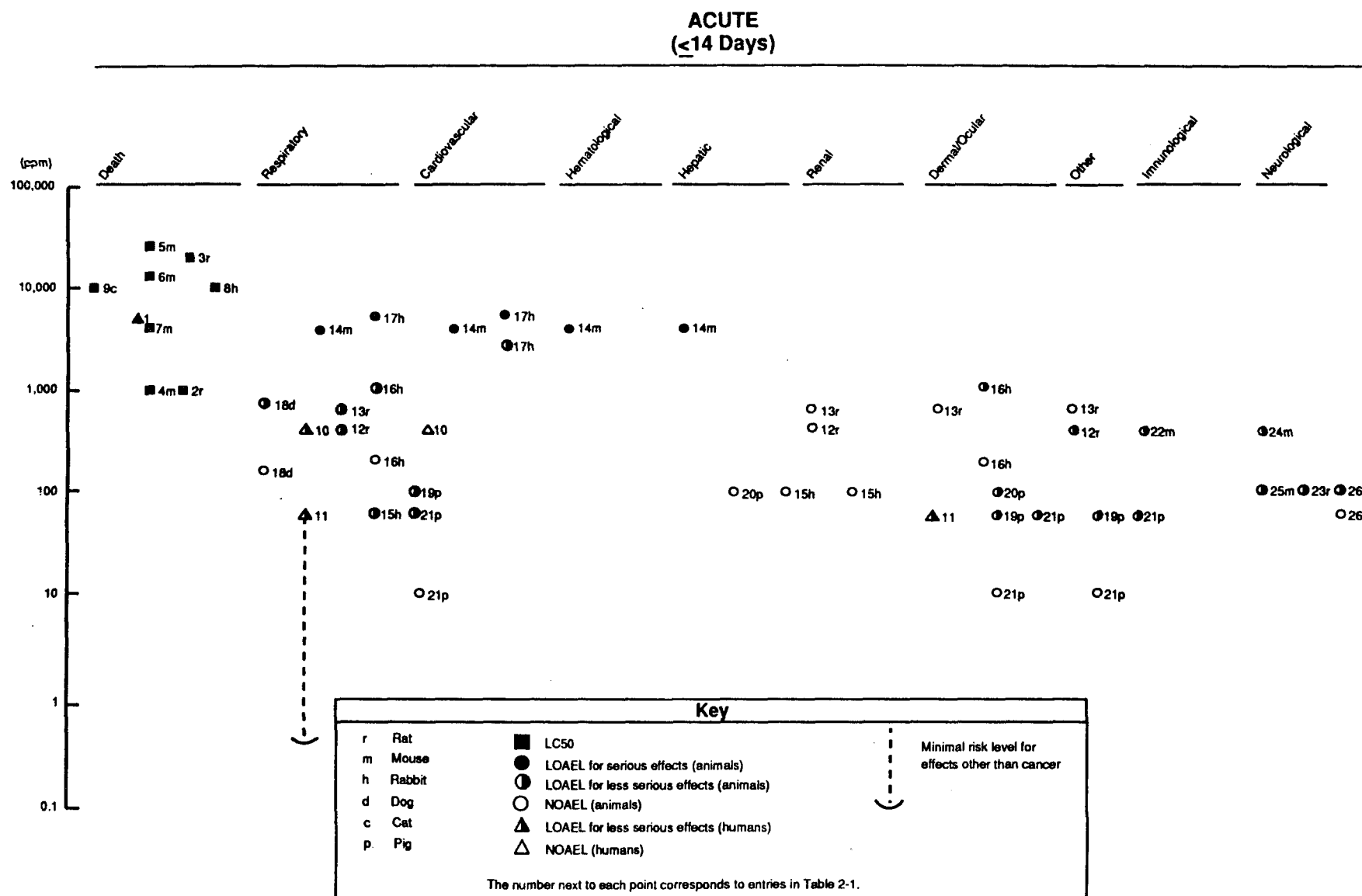


FIGURE 2-1. Levels of Significant Exposure to Ammonia - Inhalation

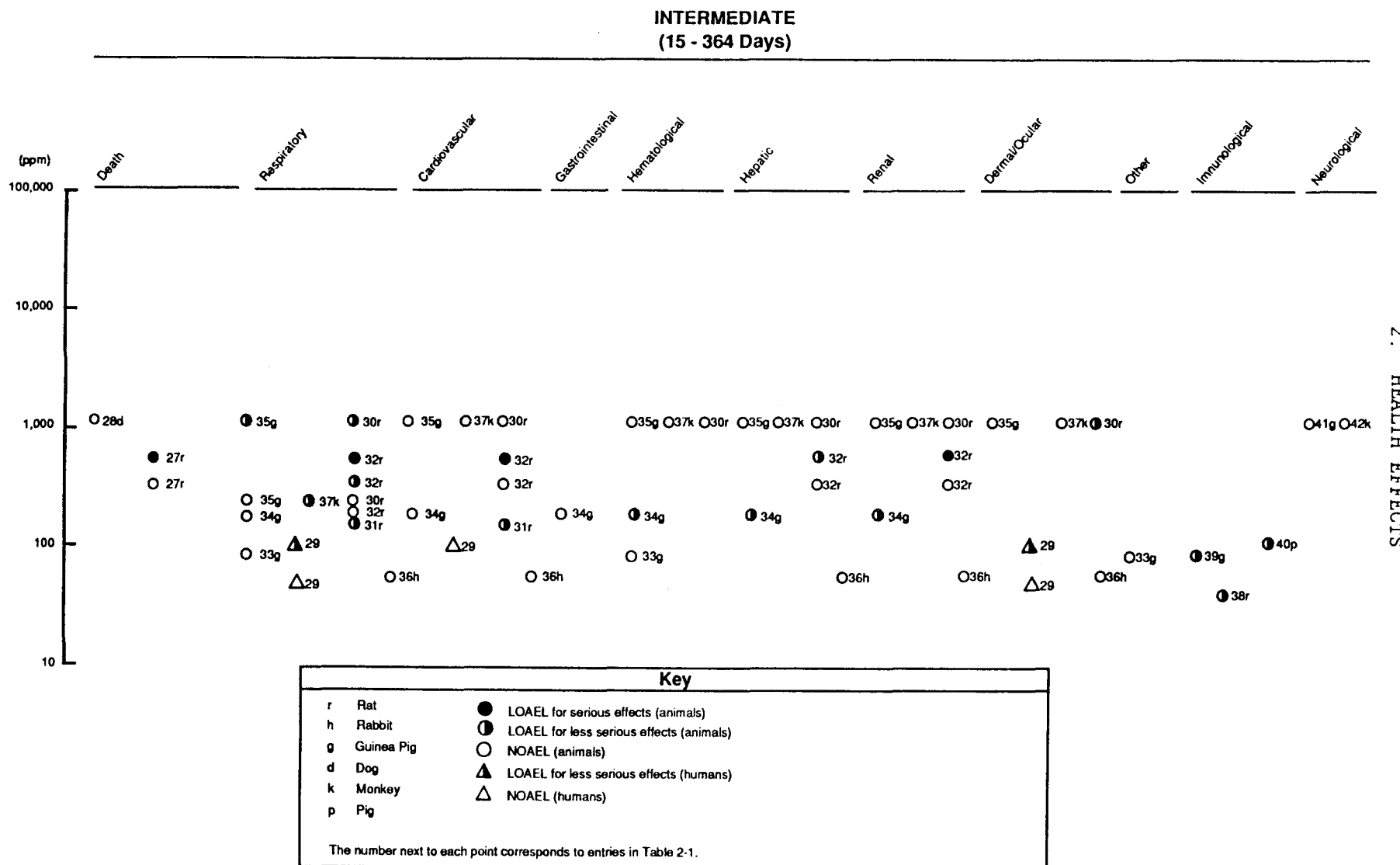


FIGURE 2-1 (Continued)

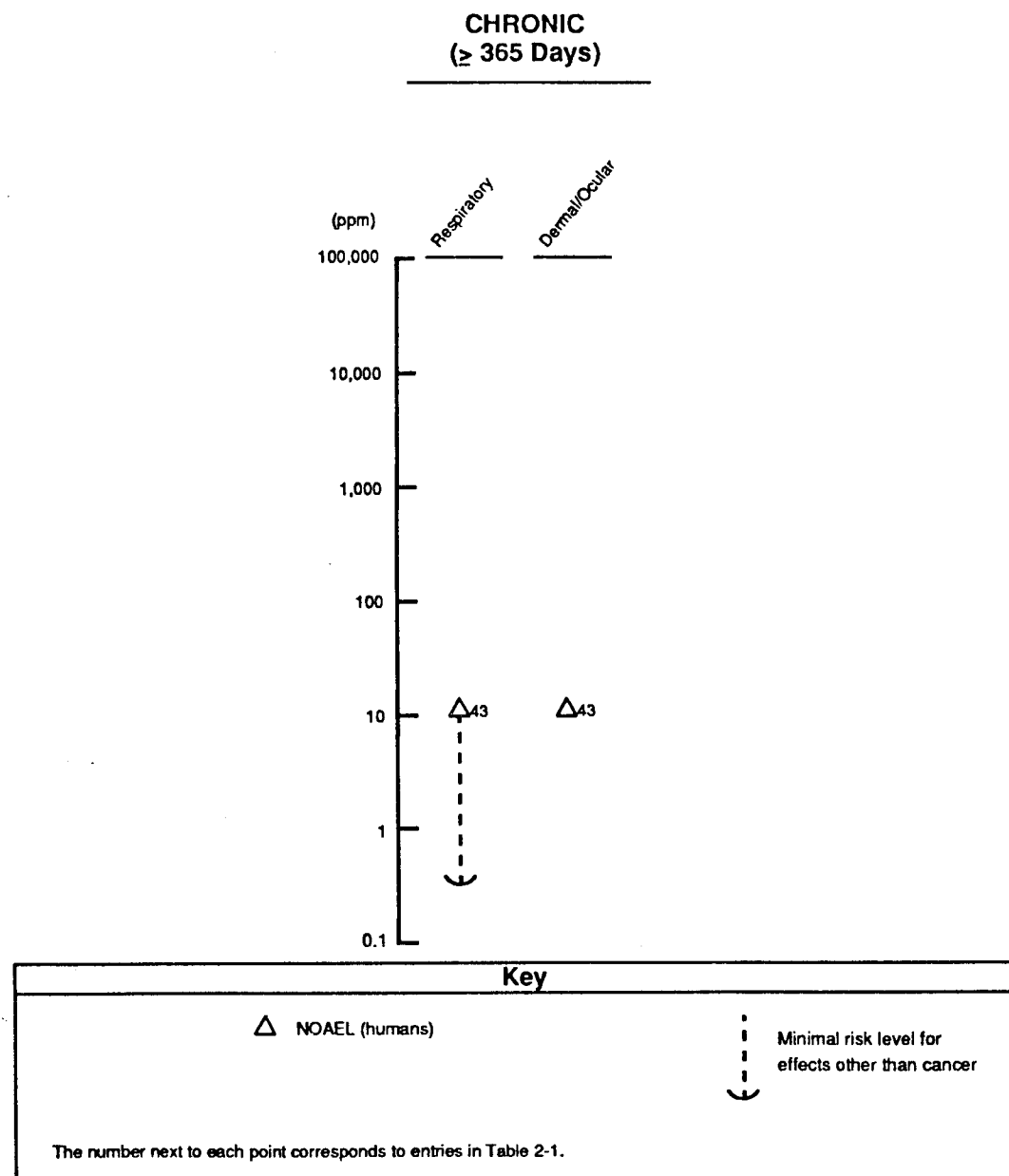


FIGURE 2-1 (Continued)

FIGURE 2-1 (Continued)

2. HEALTH EFFECTS

to the upper and lower respiratory tract and alveolar capillaries (Coon et al. 1970; Kapeghian et al. 1982; Mayan and Merilan 1972; Richard et al. 1978a,b; Schaerdel et al. 1983; Stombaugh et al. 1969). Prolonged or repeated exposures to lower levels (≥ 150 ppm) produce inflammation and lesions of the respiratory tract (Broderick et al. 1976; Coon et al. 1970). All reliable LOAELS and highest NOAELS are presented in Table 2-1 and Figure 2-1.

Cardiovascular Effects. Acute exposure to highly concentrated aerosols of ammonia may cause elevated pulse and blood pressure and cardiac arrest in humans (Hatton et al. 1979; Montague and Macneil 1980; White 1971). These effects do not occur after acute exposure to 500 ppm ammonia or repeated exposure to 100 ppm ammonia (Ferguson et al. 1977; Silverman et al. 1949).

Cardiovascular changes that may be analogous to those observed in humans have been observed in rabbits exposed to high concentrations of ammonia (Richard et al. 1978b). Bradycardia, hypertension, and cardiac arrhythmias leading to cardiovascular collapse follow acute exposures to concentrations exceeding 5000 ppm. Pathological correlates for these effects have not been demonstrated. Atrophy of pericardial fat has been observed in mice exposed to 4000 ppm ammonia (Kapeghian et al. 1982). Myocardial fibrosis has been observed in rats that died after prolonged continuous exposure to 653 ppm (Coon et al. 1970). The functional significance of these lesions have not been elucidated. Reliable LOAELS and highest NOAELS for cardiovascular effects are presented in Table 2-1 and Figure 2-1.

Gastrointestinal Effects. Exposure to highly concentrated aerosols of anhydrous ammonia can produce burns of the lips, oral cavity, and pharynx, along with edema of these areas (Hatton et al. 1979; Levy et al. 1964; Price et al. 1983; Stroud 1981; Ward et al. 1983; Yang et al. 1987). Gastrointestinal effects of ammonia in animals have not been reported. As shown in Table 2-1, pathological changes in the gastrointestinal tract were not observed in guinea pigs exposed repeatedly to 170 ppm ammonia (Weatherby, 1952).

Hematological Effects. Cyanosis, elevated white blood cell count, and pulmonary artery thrombosis have been observed in humans exposed to highly concentrated aerosols of anhydrous ammonia (Sobonya 1977; Taplin et al. 1976; Voisin et al. 1970; Ward et al. 1983; White 1971).

Standard hematological measurements, including blood hemoglobin and differential cell counts, have been reported for a few animal species. As shown in Table 2-1 and Figure 2-1, acute effects of ammonia have not been demonstrated (Doig and Willoughby 1971). Repeated exposure to 1100 ppm had no effect on hematological parameters in guinea pigs, rats, and rabbits (Coon et al. 1970). Weatherby (1952) reported increased concentrations of hemosiderin in the spleen of guinea pigs exposed to 170 ppm ammonia for

2. HEALTH EFFECTS

18 weeks. This suggests the possibility of increased turnover of red blood cells; however, this has not been corroborated.

Musculoskeletal Effects. Spasms of muscles of the extremities have resulted from acute exposure of humans to highly concentrated aerosols of anhydrous ammonia (White 1971).

Hepatic Effects. Hemorrhagic necrosis of the liver was observed in an individual exposed to a lethal concentration of ammonia vapors for a short period of time (Heifer 1971). No other cases of hepatic effects have been reported. Hepatic effects are usually not seen in animals exposed to ammonia. As shown in Table 2-1, liver necrosis has been observed following acute lethal exposure to ammonia and following continuous long-term exposure to ammonia, but not at lower, nonlethal exposure concentrations (Coon et al. 1970; Kapeghian et al. 1982; Mayan and Merilan, 1972).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to ammonia. In animals, renal effects do not appear to be an important feature of the toxicity of inhaled ammonia. Effects reported have not been corroborated or cannot be interpreted. Mild abnormalities in the renal tubules have been described in guinea pigs exposed to 170 ppm for 18 weeks; however, renal effects at this relatively low level have not been corroborated (Weatherby 1952). Exposure to more than 6 times this concentration for 6 weeks did not result in pathological changes to the kidney (Coon et al. 1970). Renal tubular calcification (severity not reported) has been reported in rats exposed to near lethal levels (Coon et al. 1970).

Dermal/Ocular Effects. Ammonia gas and aerosols of anhydrous ammonia are dermal and ocular irritants in humans and animals. These effects are described in the discussion of dermal and ocular effects associated with dermal and ocular exposure (Section 2.2.3.2).

Other Systemic Effects. A study was reported in which human subjects were exposed continuously to low levels of ammonia (3-7 ppm) for up to 37 days (Kalandarov et al. 1984). Although detailed observations were not presented, apparently this exposure was tolerated without obvious symptoms of ill health.

Reduced body weight has been observed in rats exposed to 500 ppm (Richard et al. 1978a). No effects were noted on body weight of mice or pigs within the ranges tested; however, pigs gained less weight and showed decreased appetite when exposed to 50 ppm ammonia for 4 or 5 weeks (Drummond et al. 1980; Stombaugh et al. 1969).

2.2.1.3 Immunological Effects

Secondary infections often complicate the clinical outcome of burns and respiratory lesions related to exposure to highly concentrated aerosols of

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anhydrous ammonia (Sobonya 1977; Taplin et al. 1976). However, there is no evidence that the decreased resistance represents a primary impairment of the immune system in humans. Nevertheless, as shown in Table 2-1 and Figure 2-1, studies in animals have shown that acute and long-term exposure to ammonia can decrease the resistance to bacterial infection and decrease immune response to infection. A significant increase in mortality was observed in mice exposed to ammonia for 168 hours followed by exposure to the LD₅₀ of Pasteurella multocida (Richard et al. 1978a). Exposure of rats to ammonia at 25 ppm or greater for 4-6 weeks following inoculation with Mycoplasma pulmonis intranasally significantly increased the severity of respiratory signs characteristic of murine respiratory mycoplasmosis (Broderick et al. 1976). Guinea pigs exposed to ammonia for 3 weeks developed a significant decrease in the cell-mediated immune response to challenge with a derivative of tuberculin (Targowski et al. 1984). Furthermore, the response of blood and bronchial lymphocytes to mitogens (phytohemagglutinin, concanavalin A, purified protein derivative of tuberculin) was markedly reduced.

2.2.1.4 Neurological Effects

Case reports of accident victims exposed to highly concentrated aerosols of anhydrous ammonia describe blurred vision, diffuse nonspecific encephalopathy, loss of consciousness, and decreased deep tendon reflexes (Hatton et al. 1979; White 1971). As shown in Table 2-1 and Figure 2-1, lethargy has been reported following acute exposure to lower levels (100-500 ppm). Acute exposure to low levels of ammonia (100 ppm) has been shown to depress free-access wheel running behavior in rodents (Tepper et al. 1985). This may represent avoidance of sensory or upper airway irritation, but these same effects can be seen after injection of ammonium salts (Section 2.4). No overt symptoms of neurological disorders were reported in guinea pigs or monkeys that were exposed to up to 1105 ppm ammonia for 6 weeks (Coon et al. 1970).

No information was located regarding the following effects of ammonia in humans or animals following inhalation exposure:

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

2.2.1.8 Cancer

Carcinogenic potential of ammonia by the inhalation route has not been assessed in humans or animals. One case report was found of a white male who developed epidermal carcinoma of the nasal septum 6 months after being badly burned by accidental contact with a refrigeration ammonia-oil mixture (Shimkin et al. 1954). If ammonia played a role in the development of this

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cancer, it was most likely due to dermal exposure, not inhalation, since the substance was oily. However, some of the ammonia was probably inhaled into the nasal vestibule and absorbed into nasal mucous. No other such reports were located, although other cases of inhalation exposure to ammonia from spills have been followed for more than 6 months after exposure. No information was located regarding cancer in animals following inhalation exposure to ammonia.

2.2.2 Oral Exposure

As discussed in Chapter 3, ammonia in aqueous solution exists in equilibrium with ammonium hydroxide, a weak base, which is partially ionized in water. Information available for humans exposed to ammonia by the oral route usually involved case reports of people who swallowed household ammonia (ammonium hydroxide). Studies by the oral route in animals generally have used ammonium salts or ammonium hydroxide. For these reasons, oral doses are expressed as mg NH_4^+ /kg/day, given as the particular ammonium compound.

2.2.2.1 Death

Human deaths due to ingestion of household ammonia have been reported (Klein et al. 1985; Klendshoj and Rejent 1966), but no quantitative data for oral exposure in humans were located. As shown in Table 2-2 and Figure 2-2, 303 mg ammonium/kg as ammonium chloride is a lethal dose in guinea pigs when given as single gavage dose (Koenig and Koenig 1949). Death, in this case, resulted from pulmonary edema. Cats, rabbits, and rats survived after a similar dose of ammonium (337 mg ammonium/kg given as ammonium chloride) than guinea pigs (Boyd and Seymour 1946).

2.2.2.2 Systemic Effects

Respiratory Effects. No information was located regarding respiratory effects of ammonia or ammonium compounds in humans following oral exposure. Guinea pigs that received single gavage doses of ammonium chloride developed serious respiratory effects including increased rate and depth of respiration, pulmonary edema, and death by respiratory failure (Koenig and Koenig 1949). Because the blood pH of the guinea pigs decreased after administration of ammonium chloride, adjustments in respiratory rate and depth may have been a compensatory mechanism for acidosis. Similarly, prolonged repeated doses of ammonium chloride in animals result in metabolic acidosis and compensatory changes in respiratory rate and tidal volume (Seegal 1927). The low blood pH results in increased lung ventilation, which increases the elimination of carbon dioxide from the blood, and therefore, can be considered a compensatory response to acidosis rather than a direct effect of ammonium on the lungs or respiratory center. Chloride ion from ammonium chloride probably caused the development of acidosis in the animal studies.

TABLE 2-2. Levels of Significant Exposure to Ammonia and Ammonium Compounds - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg NH ₄ ⁺ /kg/d)	LOAEL (Effect)		Reference	Form
						Less Serious (mg NH ₄ ⁺ /kg/d)	Serious (mg NH ₄ ⁺ /kg/d)		
ACUTE EXPOSURE									
Death									
1	Rat	(G)	1 d		337			Boyd and Seymour 1946	NH ₄ Cl
2	Gn Pig	(G)	1 d				303 ^a (Death due to pulmonary edema)	Koenig and Koenig 1949	NH ₄ Cl
3	Rabbit	(G)	1 d		337			Boyd and Seymour 1946	NH ₄ Cl
4	Cat	(G)	1 d		337			Boyd and Seymour 1946	NH ₄ Cl
Systemic									
5	Rat	(W)	6 d	Hemato		977 (Elevated serum calcium)		Barzel 1975	NH ₄ Cl
6	Rat	(G)	7 d	Renal Other		433 ^b (Renal enlargement) 433 (Increased enzyme)		Janicki 1970	NH ₄ Cl
7	Gn Pig	(G)	1 d	Resp			303 ^a (Pulmonary edema)	Koenig and Koenig 1949	NH ₄ Cl
INTERMEDIATE EXPOSURE									
Systemic									
8	Rat	(W)	90 d 6 d/wk	Cardio Gastro Hemato Hepatic Renal Other	79 79 79 79 79 40 ^{c,d}	79 ^e (Reduced food intake, reduced body weight)		Gupta et al.	NH ₄ NH ₂ SO ₃
9	Rat	(W)	3 wk	Renal	412			Freedman and Beeson 1961	NH ₄ Cl

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg NH ₄ ⁺ /kg/d)	LOAEL (Effect)		Reference	Form
						Less Serious (mg NH ₄ ⁺ /kg/d)	Serious (mg NH ₄ ⁺ /kg/d)		
10	Rabbit	(G)	234 d	Resp			14,722 (Decreased respiratory rate, increased respiratory volume)	Seegal 1927	NH ₄ CL
				Musc/skel			14,722 (Osteoporosis)		
				Renal			14,722 (Swollen tubular epithelium; tubular degeneration)		
11	Rabbit	(G)	36 d	Renal			2377 ^f (Tubular epithelium swollen, slight spontaneous nephritis)	Seegal 1927	NH ₄ CL
12	Rabbit	(G)	17 mo	Cardio			124 ^g (Altered blood pressure)	Fazekas 1939	NH ₄ OH
				Other			124 ^g (Enlarged adrenal glands; altered bw)		
13	Rabbit	(G)	18 d	Renal	1558			Seegal 1927	NH ₄ CL
14	Dog	(G)	11 wk	Musc/skel			337 ^h (Bone deformity and softening)	Bodansky et al. 1932	NH ₄ CL
CHRONIC EXPOSURE									
Systemic									
15	Rat	(W)	330 d	Musc/skel		991 (Bone loss)		Barzel and	NH ₄ CL
				Other		991 (Reduced bw)		Jowsey 1969	

^aConverted to an equivalent concentration of 1192 ppm in drinking water for presentation Table 1-4.

^bConverted to an equivalent concentration of 3093 ppm in drinking water for presentation in Table 1-4.

^cUsed to derive intermediate oral MRL of 0.3 NH₄⁺/kg/d; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability).

^dThis MRL has been converted to an equivalent concentration in water (10 ppm) for presentation in Table 1-3.

^eConverted to an equivalent concentration of 564 ppm in drinking water for presentation in Table 1-4.

^fConverted to an equivalent concentration of 21,609 ppm in drinking water for presentation in Table 1-4.

^gConverted to an equivalent concentration of 1127 ppm in drinking water for presentation in Table 1-4.

^hConverted to an equivalent concentration of 7027 ppm in drinking water for presentation in Table 1-4.

bw = body weight; Cardio = cardiology; d = day; (G) = gavage; Gastro = gastrointestinal; Gn Pig = guinea pig; Hemato = hematological; kg = kilogram; mo = month; Musc/skel = muscular/skeletal; NH₄Cl = ammonium chloride; NH₄OH = ammonium hydroxide; NH₄NH₂SO₃ = ammonium sulfamate; Resp = respiratory; (W) = water; wk = week.

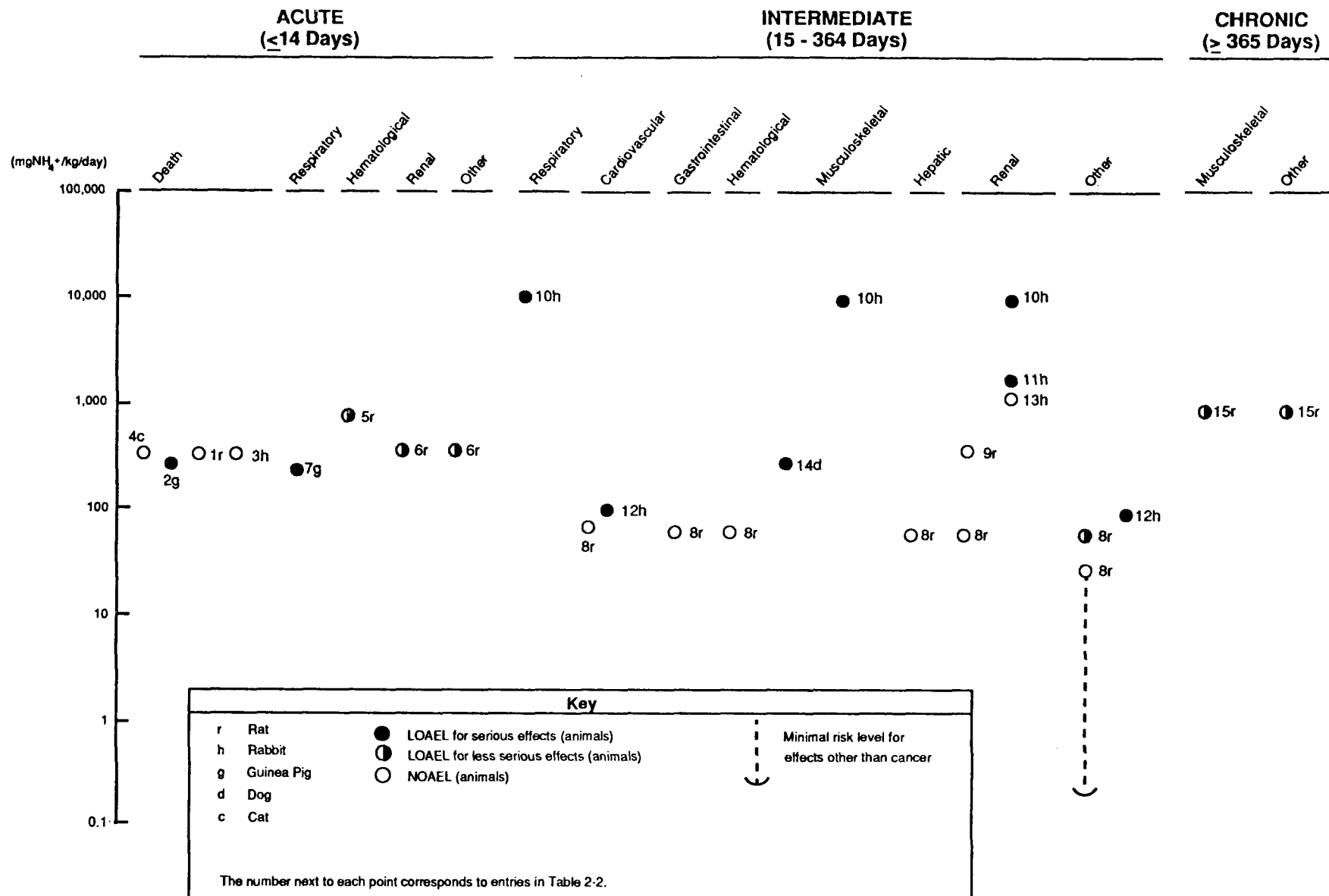


FIGURE 2-2. Levels of Significant Exposure to Ammonia and Ammonium Compounds - Oral

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Cardiovascular Effects. No information was located regarding cardiovascular effects of ammonia or ammonium compounds in humans following oral exposure. No pathological abnormalities were noted in the hearts of adult and weanling rats fed doses of up to 79 mg ammonium/kg/day as ammonium sulfamate for 90 days in drinking water (Gupta et al. 1979). Repeated gavage doses of 124 mg ammonia/kg/day as ammonium hydroxide for 17 months in rabbits resulted in an initial drop in blood pressure, followed by a gradual rise of 10-30 mmHg above baseline levels (Fazekas 1939). These data are presented in Table 2-2 and Figure 2-2.

Gastrointestinal Effects. Children who bit into aromatic ammonia spirits capsules responded by vomiting and drooling, and suffered burns of the oral and pharyngeal areas (Lopez et al. 1988). Esophageal lesions and edema were reported in three persons who ingested household ammonia (ammonium hydroxide) (Klein et al. 1985). These observations were not quantified. The effects are probably due to the alkaline nature of ammonium hydroxide. As shown in Table 2-2 and Figure 2-2, no histopathological abnormalities of the gastrointestinal tract were observed in adult or weanling rats administered doses of up to 74.8 mg ammonium/kg/day as ammonium sulfamate for 90 days via drinking water (Gupta et al. 1979).

Hematological Effects. No information was located regarding the hematological effects of ammonia or ammonium compounds in humans following oral exposure. Repeated exposure to ammonium chloride in animals resulted in metabolic acidosis and related changes in bone metabolism and serum calcium. For example, rabbits fed diets containing high levels of ammonium chloride had increased serum calcium (Barzel, 1975). The increased serum calcium resulted from enhanced demineralization of bone in response to chronic acidosis. This effect was not found to be a specific effect of ammonium and was reported to occur in states of chronic metabolic acidosis produced from repeated doses of acidifying agents (e.g., hydrochloric acid, sulfuric acid). As shown in Table 2-2 and Figure 2-2, no effects on blood hemoglobin or blood cell counts were observed in adult or weanling rats that received doses of up to 79 mg ammonium/kg/day administered as ammonium sulfamate in drinking water (Gupta et al. 1979).

Musculoskeletal Effects. No information was located regarding musculoskeletal effects of ammonia or ammonium compounds in humans following oral exposure. Guinea pigs and rats that received lethal gavage doses of ammonium chloride developed muscle weakness, fasciculation, and incoordination (Koenig and Koenig 1949). In other animal studies, repeated exposure to ammonium salts resulted in metabolic acidosis, which stimulated bone demineralization. As is shown in Table 2-2 and Figure 2-2, repeated exposure to ammonium chloride in drinking water resulted in net bone resorption in rabbits and bone deformities in dogs (Barzel and Jowsey 1969; Bodansky et al. 1932; Seegal 1927). This effect can be anticipated with repeated exposure to any acidifying agent.

2. HEALTH EFFECTS

Hepatic Effects. No information was located regarding hepatic effects of ammonia or ammonium compounds in humans following oral exposure. As shown in Table 2-2 and Figure 2-2, no toxic effects were noted in livers of adult or weanling rats fed doses of up to 79 mg ammonium/kg/day as ammonium sulfamate for 90 days in drinking water (Gupta et al. 1979).

Renal Effects. Renal failure was identified as the cause of death in humans after ingestion of an unknown amount of household ammonia (ammonium hydroxide) (Klein et al. 1985). It is not certain if this represents a primary effect of ammonium or is secondary to massive burns to the gastrointestinal tract.

Renal effects have been observed in animals following repeated oral doses of ammonium chloride. These effects may be secondary to chronic acidosis produced from the chloride ion rather than from a direct effect of ammonia on the kidney. Renal enlargement, increased ammonia content, or increased urinary ammonia, have been reported in rats (Benyajati and Goldstein 1975; Janicki 1970; Lotspeich 1965;), but are unlikely to be indicative of renal pathology. Renal tubular swelling, slight spontaneous nephritis, and acidosis have been observed in rabbits (Seegal 1927). The highest NOAELs and LOAELs are presented in Table 2-2 and Figure 2-2.

Dermal/Ocular Effects. No information was located regarding dermal or ocular effects of ammonia or ammonium compounds in humans or animals following oral exposure.

Other Systemic Effects. Other systemic effects that have been observed in animals including enlarged adrenal glands (Fazekas 1939) and decreased body weight or weight gain (Barzel and Jowsey 1969; Gupta et al. 1979; Noda and Chikamori 1976). NOAELs and LOAELs for these effects are reported in Table 2-2 and Figure 2-2. Enlarged adrenal glands were observed in rabbits that received 124 mg ammonium/kg/day as ammonium hydroxide by gavage in water for 17 months (Fazikas 1939). Gupta et al. (1979) noted increased water intake and reduced food intake in weanling rats, and decreased body weight in adults but not weanlings fed 79 mg ammonium/kg/day in drinking water for 90 days as ammonium sulfamate. This represents the LOAEL for this effect. A NOAEL of 40 mg ammonium/kg/day was also identified in this study (see Tables 1-3, 1-4, and 2-2, and Figure 2-2). Based on this value, an intermediate oral MRL of 0.3 mg ammonium/kg/day was calculated as described in the footnote in Table 2-2.

2.2.2.3 Immunological Effects

No information was located regarding immunological effects of ammonia or ammonium compounds in humans or animals after oral exposure.

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2.2.2.4 Neurological Effects

No information was located regarding neurological effects of ammonia or ammonium compounds in humans after oral exposure.

Guinea pigs and rats that received lethal gavage doses of ammonium chloride developed neuromuscular effects including fasciculation; incoordination; hyperexcitability to tactile, auditory, and painful stimuli; and tonic convulsions (Koenig and Koenig 1949).

No information was located regarding the following effects of ammonia or ammonium compounds in humans or animals following oral exposure:

2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

2.2.2.8 Cancer

No information was located regarding carcinogenic effects of ammonia or ammonium compounds in humans following oral exposure. Exposure of mice to 193 mg ammonium/kg/day as ammonium hydroxide in drinking water for 2 years did not produce carcinogenic effects, nor did it affect spontaneous development of breast cancer that is common to C₃H female mice (Toth 1972). No evidence of a carcinogenic effect was found in mice treated by gavage with ammonia dissolved in water alone at a dose of 42 mg/kg/day for 4 weeks or with diethyl pyrocarbonate alone, but 9/16 mice treated with a combination of ammonia and pyrocarbonate developed lung tumors. The ammonia and pyrocarbonate may have reacted in vivo to form the carcinogen, urethane, which produced lung tumors in 9/9 of the mice (Uzvolgyi and Bojan 1980). No lung tumors were observed in the offspring of mice exposed similarly to ammonia and diethyl pyrocarbonate during pregnancy or during lactation (Uzvolgyi and Bojan 1985).

2.2.3 Dermal Exposure

Dermal exposure to ammonia may also result in some inhalation exposure. Therefore, based on the available data, it is not always clear to what extent each route of exposure contributes to the toxicity observed in dermal exposure studies.

2.2.3.1 Death

Human and animal deaths involving dermal and ocular exposure to ammonia have been reported (Prokop'eva et al. 1973; Slot 1938; Sobonya 1977), but extent of exposure is not known, and effects are probably due to inhalation exposure, as well. These data are presented in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to Ammonia - Dermal

Species	Exposure Frequency/ Duration	Effect	NOAEL	LOAEL (Effect)		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rat	1 d 30 min/d				71.9 mg/L (LC ₅₀)	Prokop'eva et al. 1973
Rat	1 d 60 min/d				48.4 mg/L (LC ₅₀)	Prokop'eva et al. 1973
Systemic						
Pig	5 wk NS	Derm/oc	10 ppm	50 ppm (Oc irritation)		Stombaugh et al. 1969
INTERMEDIATE EXPOSURE						
Systemic						
Human	6 wk 5 d/wk 6 hr/d	Derm/oc		100 ppm (Transitory eye irritation)		Ferguson et al. 1977

d = day; Derm/oc = Dermal/ocular; LC₅₀ = lethal concentration, 50% kill; min = minute; NS = not specified; wk = week.

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2.2.3.2 Systemic Effects

Dermal exposure to ammonia has produced respiratory, cardiovascular, gastrointestinal, renal, and dermal/ocular effects.

Respiratory Effects. Respiratory effects have been reported in humans from exposure to massive amounts of ammonia vapor, but no quantitative data were located. It is also unclear as to what extent the effects were a result of inhalation exposure. Tracheitis, bronchitis, edema, and bronchopneumonia were reported by Slot (1938). Lung infection and respiratory distress were reported in one case (Sobonya 1977). Dyspnea, rales, rhonchi, and blocked airways were found by Levy et al. (1964). The effects probably resulted from concurrent inhalation exposure. No information was located regarding respiratory effects of ammonia in animals following dermal or ocular exposure.

Cardiovascular Effects. Elevated pulse, shock, and cardiac failure were reported in humans from accidental exposures to massive amounts of ammonia gas, but the extent of exposure was not quantified (Slot 1938). No information was located regarding cardiovascular effects of ammonia in animals following dermal or ocular exposure.

Gastrointestinal Effects. Persistent vomiting was noted by Slot (1938) in human accidental massive exposure cases, but the extent of exposure was not quantified. Oral and pharyngeal burns and edema were reported by Levy et al. (1964) in four human males accidentally exposed to an unknown quantity of anhydrous ammonia.

Renal Effects. Renal congestion and hemorrhagic nephritis were reported by Slot (1938) in six cases of accidental human exposures to highly concentrated aerosols of ammonia (anhydrous ammonia). The exposure level cannot be determined from the available data.

Dermal/Ocular Effects. Skin and eyes are extremely sensitive to airborne ammonia or ammonia dissolved in water. The topical damage caused by ammonia is probably due mainly to its alkali properties. Its high water solubility allows it to dissolve in moisture on these surfaces, react with fatty substances in the corneal layer, be absorbed into deeper layers and inflict extensive damage (Jarudi and Golden 1973). Reports of skin damage in humans are numerous, but good quantitative data are lacking. The severity of the damage is proportional to concentration and duration of exposure; flushing with water immediately after contact alleviates or prevents effects. Burns, blisters, and lesions of the skin have been reported (Close et al. 1980; Flury et al. 1983; Shimkin et al. 1954; Slot 1938; Taplin et al. 1976). Exposure levels associated with dermal/ocular effects are presented in Table 2-3.

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Reported ocular effects in humans following ammonia exposure increase in severity with dose and duration. Good quantitative data are lacking, but symptoms progress as follows: inflamed eyes, lacrimation, swelling of the eyelids (Beare et al. 1988; Caplin 1941; Close et al. 1980; Ferguson et al. 1977; Jarudi and Golden 1973; Legters et al. 1981; Montague and Macneil 1980; Price et al. 1983; Silverman et al. 1949; Stombaugh 1969; Verberk 1977; Ward et al. 1983), hyperemic conjunctiva (Caplin 1941; Hatton et al. 1979; Levy et al. 1964; Slot 1938; Sobonya 1977), and sustained corneal damage (Caplin 1941; Grant 1974; McGuinness 1969; Stroud 1981; Yang et al. 1987). Ammonia is slightly irritating to human eyes at concentrations of 100 ppm (Ferguson et al. 1977), and immediately irritating to the eyes and throat at 698 ppm (Henderson and Haggard 1927). Exposure to an air concentration of 250 ppm is bearable for most persons for 30-60 minutes (Withers et al. 1986).

Animal data regarding dermal and ocular effects of exposure to ammonia support the findings in humans. Corneal opacity has been observed in rabbits following brief exposures (2 seconds) to a solution of 28.5% ammonium hydroxide (Grant 1974). Volume administered was not reported.

2.2.3.3 Immunological Effects

Secondary infections often complicate the clinical outcome of burns and respiratory lesions related to exposures to highly concentrated aerosols of anhydrous ammonia in which dermal and ocular exposure accompanies inhalation exposure (Sobonya 1977; Taplin et al. 1976). However, there is no evidence that the decreased resistance represents a primary impairment of the immune system in humans. No information was located regarding the immunological effects of ammonia in animals following dermal or ocular exposure.

No information was located regarding the following effects of ammonia in humans or animals following dermal or ocular exposure:

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

Carcinogenic potential of ammonia has not been established in humans or animals by the dermal route of exposure. One case report was found of a white male who developed epidermal carcinoma of the nasal septum 6 months after being badly burned by accidental contact with a refrigeration ammonia oil mixture (Shimkin et al. 1954). It is unclear whether ammonia played a role in this tumor development. No other reports were located, although

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many cases of contact with ammonia from spills have been followed for more than 6 months after exposure.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Experiments with volunteers show that ammonia, regardless of its tested concentration in air (range = 57-500 ppm), is almost completely retained in the nasal mucosa (83-92%) during short-term exposure, i.e., up to 120 seconds (Landahl and Herrmann 1950). Longer-term exposure (10-27 minutes) to a high concentration (500 ppm) results in decreased retention (4-30%), with 350-400 ppm excreted in expired air by the end of the exposure period (Silverman et al. 1949); this suggests an adaptive capability or saturation of the absorptive process. Nasal and pharyngeal irritation, but not tracheal irritation, suggests that ammonia is retained in the upper respiratory tract. Unchanged levels of blood-urea-nitrogen (BUN), nonprotein nitrogen, urinary-urea, and urinary-ammonia are evidence of low absorption into the blood. Exposure to common occupational limits of ammonia in air (26 ppm) with 30% retention (and assuming this quantity is absorbed into the blood stream) would yield an increase in blood-ammonia concentration of 0.09 mg/L (calculated by WHO 1986). This calculated rise is only 10% above fasting levels, as reported by Conn (1972).

Animal data provide supporting evidence for high-percentage nasal retention, thus protecting the lower respiratory tract from exposure [Dalhamn (1963) and Boyd et al. (1944), rabbit; Egle (1973), dog]. Rats exposed to concentrations up to 32 ppm showed no increase in blood ammonia levels; exposures of 310-1157 ppm led to significantly increased blood concentrations of ammonia within 8 hours post-exposure, but levels returned to normal within 12 hours of continuous exposure and remained so over the 24-hour treatment period. This suggests an adaptive response mechanism may be activated with longer-term exposure (Schaerdel et al. 1983).

2.3.1.2 Oral Exposure

Case reports of human ingestion of household ammonia (ammonium hydroxide) provide evidence of its absorption by this route, but few provide quantitative data. In one case, analysis of contents of stomach and blood showed ammonia concentrations of 153 and 33 ppm, respectively (Klendshoj and Rejent 1966); it is not known how much was swallowed. Human ingestion of ammonium chloride tablets (1.29-2.86 mg/kg/day) led to a small transient increase (33% above fasting levels) in arterial blood concentrations of ammonia among 55% (11/20) of healthy subjects. No change was noted in the remaining nine subjects in this group, but among 50 cirrhotic patients greater increases were noted, and return to normal levels was slow. These data indicate that ingested ammonia is readily absorbed from the digestive

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tract, and that the liver plays a large role in removing it from the blood (Conn 1972). Analysis of urine samples from subjects on high and low protein diets suggest that 30-65% of labeled nitrogen from ^{15}N -ammonium chloride is absorbed and metabolized (Richards et al. 1975).

Ammonia is endogenously produced in the human digestive tract, much of it arising from the bacterial degradation of nitrogenous compounds from ingested food. About 4200 mg/day are produced, greater than 70% of which is synthesized or liberated within the colon and its fecal contents. The total amount absorbed is about 4150 mg/day, or 99% (Summerskill and Wolpert 1970); absorption after oral loading is similarly complete (Furst et al. 1969). Evidence from Castell and Moore (1971) and Mossberg and Ross (1967) suggests that absorption of ammonia increases with increase of pH of the contents of the lumen, and that the ammonium ion is actively transported at the lower pH levels (pH 5 was lowest detected absorption). Ammonia absorbed from the gastrointestinal tract travels via the hepatic portal vein directly to the liver, where in healthy individuals most of it is converted to urea and glutamine. Human and animal data show that little of it normally reaches the systemic circulation as ammonia or ammonium compounds, but that it is a normal constituent of plasma at low levels (Brown et al. 1957; Pitts 1971; Salvatore et al. 1963; Summerskill and Wolpert 1970). Analysis of plasma drawn from ten healthy young male subjects yielded endogenously derived ammonia concentrations ranging from 30-55 $\mu\text{g NH}_3/100\text{ mL}$, with a mean of 39 $\mu\text{g}/100\text{ mL}$ (Brown et al. 1957).

2.3.1.3 Dermal Exposure

Quantitative data on absorption from exposure by the dermal route were not located in the available literature. Human case reports of dermal exposure describe local damage (burns, irritations). One report of case histories of five persons exposed to an exploding, bursting anhydrous ammonia gas pipe indicated there was systemic toxicity (vomiting, renal congestion, delirium), but exposure was by inhalation as well as dermal route, and it is impossible to delineate a systemic dermal exposure contribution (Slot 1938).

WHO (1986) concluded that systemic effects from skin and eye exposure are not quantitatively important. Ammonia is readily absorbed into the eye; it was found to diffuse within seconds into cornea, lens, drainage system, and retina (Beare et al. 1988; Jarudi and Golden 1973). However, amounts absorbed were not quantified, and absorption into systemic circulation was not investigated.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No quantitative reports of distribution of ammonia from inhalation exposure were found in the available literature. Absorption data from

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human inhalation exposure suggest that only small amounts of ammonia are absorbed into the systemic circulation (Silverman et al. 1949; WHO 1986). Most of the quantities retained in the upper respiratory tract are excreted in expired air within 30 minutes (Silverman et al. 1949). The lack of change in blood nitrogen compounds and urinary-ammonia compounds lends further support to this (Silverman et al. 1949). Toxic effects reported from inhalation exposure suggest local damage, or changes resulting from necrotic tissue degradation, rather than presence of elevated levels of ammonia, per se, in tissues other than the respiratory/pharyngeal tissues. Information on the distribution of endogenously-produced ammonia suggests that any ammonia absorbed through inhalation would be distributed to all body compartments via the blood, where it would be used in protein synthesis or as a buffer, and that excess levels would be reduced to normal by urinary excretion, or converted by the liver to glutamine and urea. If present in quantities that overtax these organs, ammonia is distributed to other tissues and is known to be detoxified in the brain (Takagaki et al. 1961; Warren and Schenker 1964).

2.3.2.2 Oral Exposure

Human oral exposure data for ammonia clearly indicate that it readily enters the portal circulation and is delivered to the liver (Conn 1972; Furst et al. 1969), as has been shown to be the case for endogenously produced ammonia (Pitts 1971; Summerskill and Wolpert 1970). In nitrogendeficient persons, oral administration of ammonia led to its incorporation into tissue proteins after having been detoxified by the liver and distributed systemically as nonessential nitrogen for protein synthesis (a nontoxic form). In these cases, output of urea from the liver corresponded to the amount of ammonia ingested (Furst et al. 1969).

Un-ionized ammonia is freely diffusible, whereas the ammonium ion is less so and is relatively confined to the extracellular compartment (Stabenau et al. 1959). However, ammonium ion is in dynamic equilibrium with dissolved ammonia. Therefore, ammonium compounds that enter the circulatory system or other body fluids can thus freely penetrate tissue cells as ammonia. Animal data indicate that within 72 hours after ingestion, labeled protein from ¹⁵N-ammonium citrate was found in liver, kidney, spleen, heart, and muscle (Vitti et al. 1964). This supports the Furst et al, (1969) finding that ammonia and its liver metabolites distribute throughout the body.

2.3.2.3 Dermal Exposure

No quantitative data on distribution of ammonia from dermal exposure were located in the available literature. Toxic effects from dermal exposure suggest that little or no ammonia gains entry into the systemic circulation by this route.

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2.3.2.4 Other Routes of Exposure

After intraperitoneal injection of ammonium chloride in mice, ammonia distributes to brain tissues within 20 seconds (Warren and Schenker 1964), and in rats, brain concentrations increase dramatically within 5 minutes (Salvatore et al. 1963). Tissues other than blood and brain were not analyzed by these researchers. Comparative patterns of distribution of ^{15}N -labeled ammonium citrate indicate that the amount of ammonia taken up by tissues other than the liver is greatest by subcutaneous injection, less by intraperitoneal injection, and least following intragastric exposure. That which gains entry into the general circulation is distributed to cells throughout the body and incorporated into tissues (Furst et al. 1969; Vitti et al. 1964). Intravenous administration of ^{15}N -labeled ammonium salts leads to rapid distribution of ^{15}N -labeled metabolites throughout the body, with the highest levels of labeled urea appearing in the kidney and liver, and lesser amounts in heart, spleen, brain, testes, and carcass. Highest levels of labeled glutamine were found in heart and liver, with lesser amounts in brain, spleen, carcass, kidney, and testes (Duda and Handler 1958).

2.3.3 Metabolism

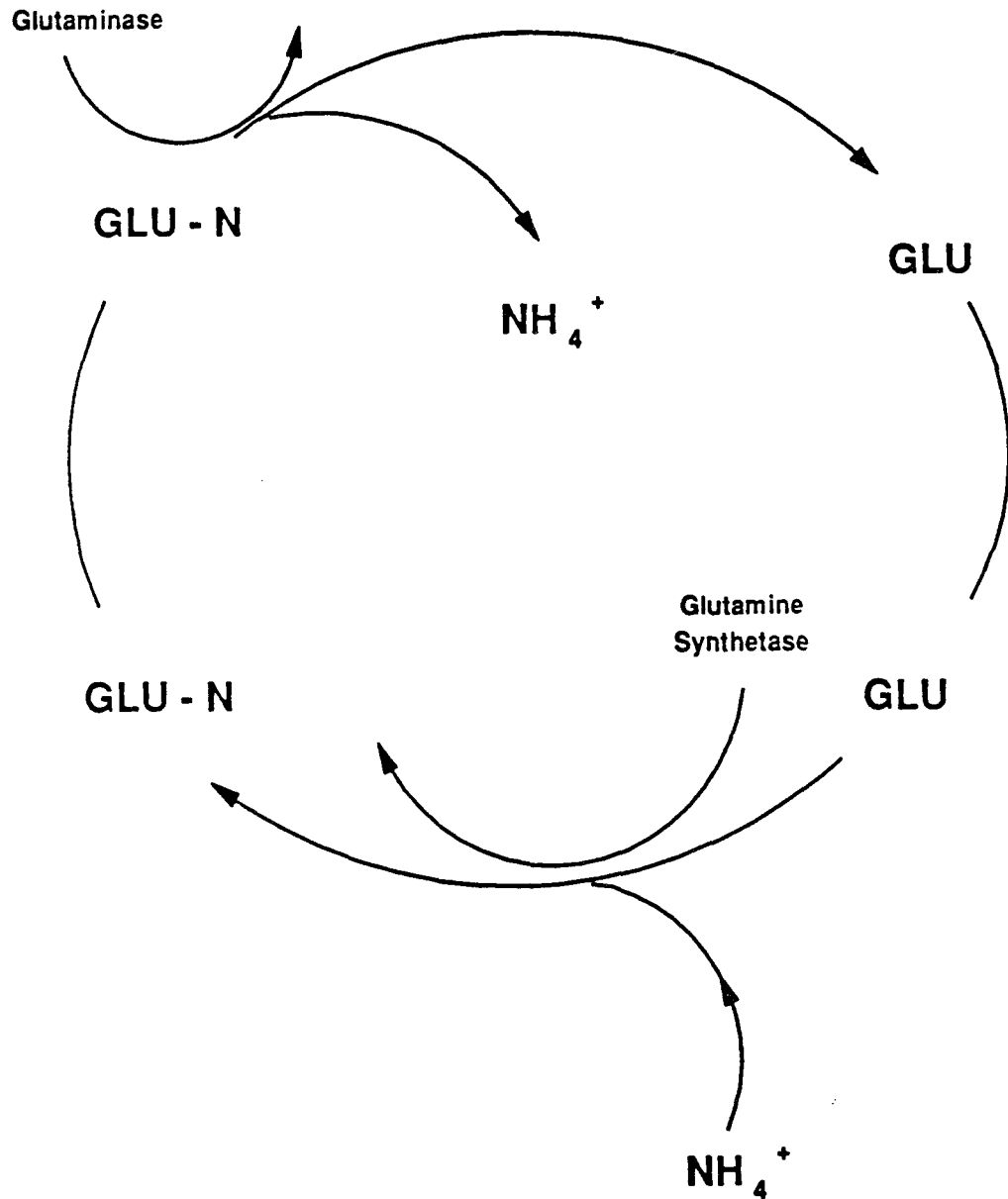
Quantitative data on human metabolism of exogenously introduced ammonia were not located in the available literature. Ammonia is metabolized to urea and glutamine mainly in the liver by the process diagrammed in Figures 2-3 and 2-4 and described by Furst et al. (1969) and Pitts (1971). However, it can be rapidly converted to glutamine in the brain and other tissues, as well (Takagaki et al. 1961; Warren and Schenker 1964). The nitrogen is released from glutamine within tissue cells and used for protein synthesis as needed (Duda and Handler 1958; Furst et al. 1969; Richards et al. 1975; Vitti et al. 1964). Ingestion of ammonium salts leads to almost complete conversion of ammonium to urea in the liver, whereas exposure by other routes may lead to its metabolism in body tissues to glutamine or tissue protein (Furst et al. 1969; Vitti et al. 1964). Duda and Handler (1958) administered 0.03 mg/kg body weight of ^{15}N -ammonium acetate intravenously and noted that 90% was converted to glutamine and urea within 30 minutes, with glutamine being the major early product. Labeled nitrogen was also found in amino acids, purines, pyrimidines, and other nitrogenous compounds. Low, but significant amounts (0.008% of a 17 mg oral dose) of ^{15}N -ammonium chloride administered repeatedly to rats were converted to ^{15}N -nitrate in the urine (Saul and Archer 1984).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Ammonia that is inhaled is temporarily dissolved in the mucous of the airway, then a high percentage of it is released back into the expired air. Silverman et al. (1949) found that 70-80% of inspired ammonia was excreted

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Source: Brunner and Thaler 1981

FIGURE 2-3. Glutamine Cycle

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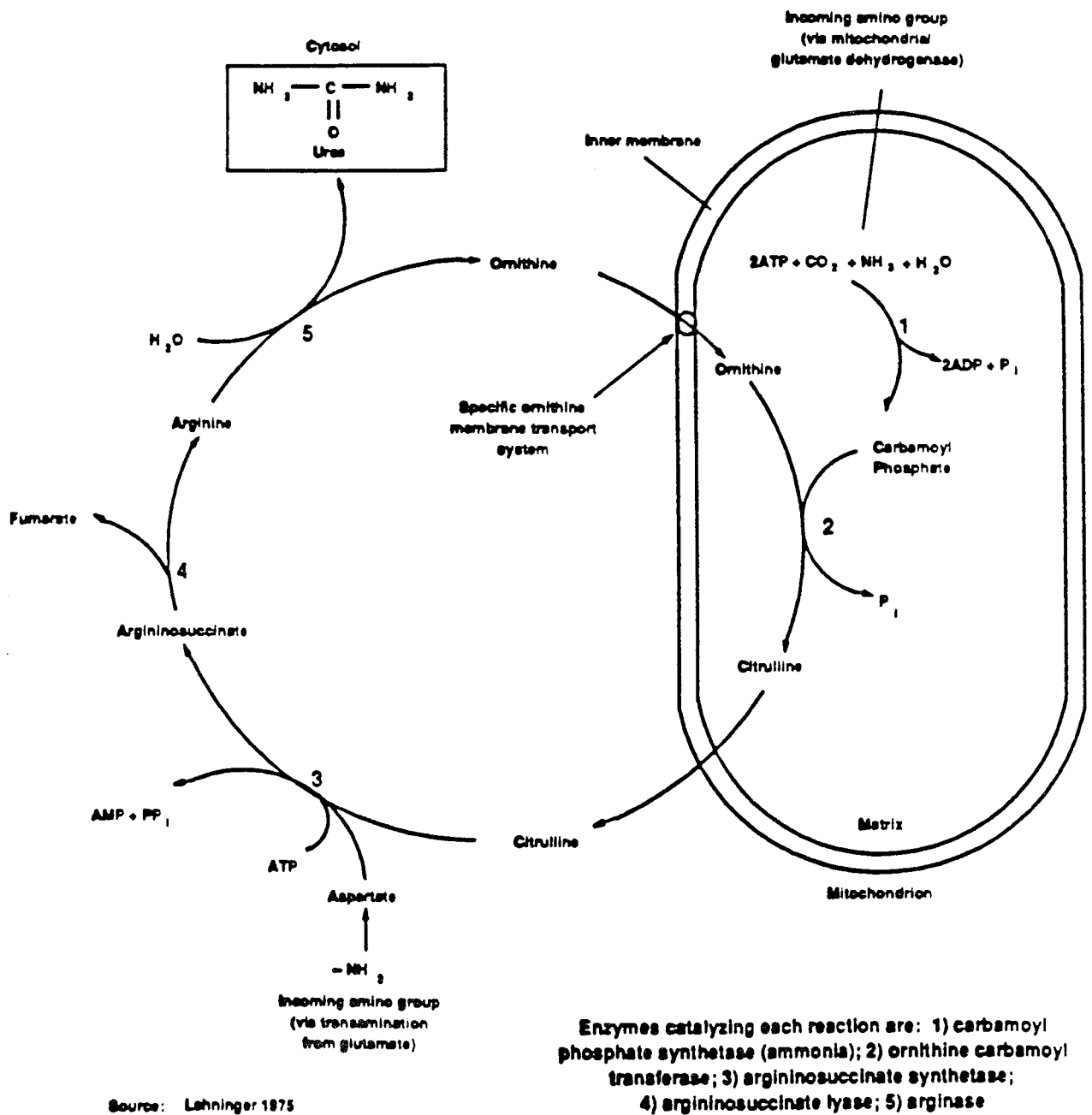


FIGURE 2-4. The Urea Cycle Showing the Compartmentalization of its Steps Within Liver Cells

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by healthy male subjects by this route following exposure to 500 ppm of ammonia for 10-27 minutes. Analysis of endogenous ammonia levels in the expired air of rats showed concentrations ranging from 10-353 ppb (mean = 78 ppb) in nose-breathing animals (Barrow and Steinhagen 1980).

The quantitative difference between inspired and expired ammonia suggests that small amounts are absorbed across the pulmonary membrane into the systemic circulation. Absorbed ammonia is excreted by the kidneys as urea and urinary ammonium compounds (Gay et al. 1969; Pitts 1971; Richards et al. 1975; Summerskill and Wolpert 1970), as urea in feces (Richards et al. 1975), and as components of sweat (Guyton 1981; Wands 1981), but quantitative data are lacking. Figures 2-3 and 2-4 illustrate the pathways by which ammonia is biotransformed. Toxic levels do not develop as a result of chronic inhalation exposure; the body has multiple effective mechanisms for detoxifying and excreting it.

2.3.4.2 Oral Exposure

The metabolic conversion is illustrated in Figures 2-3 and 2-4. Excretion data for humans orally exposed to ammonia have been quantified with respect to excretion of isotope from ^{15}N -labeled ammonium salts, thus providing an indication of the turnover rate of the compound within the body and excretion route of its metabolites. Approximately 72% of a dose of ^{15}N was excreted in the urine of three subjects within 3 days of ingestion of ammonium salts in drinking water; 25% (24% urinary urea and 1% urinary ammonia) was eliminated within the first 6 hours after exposure. Ammonium salt administered by gavage to humans led to a corresponding increase in blood urea concentration transported out of the liver (Furst et al. 1969); the authors concluded that orally ingested ammonium salt is quickly and almost completely converted in the liver and eliminated from the body as urinary urea. Analysis of urine samples from subjects on high and low protein diets showed higher cumulative excretion of ^{15}N (% of dose) in the urine of the high protein group (approximately 70%) than that of the low protein group (35%). Small amounts of labeled nitrogen were also excreted as urea in feces (Richards et al. 1975).

These data correspond to that for excretion of endogenously produced ammonia (Davies and Yudkin 1952; Muntwyler et al. 1956; Summerskill and Wolpert 1970; Van Slyke et al. 1943). Ammonia is also known to be excreted via sweat (Guyton 1981; Wands 1981) and expired air (Barrow and Steinhagen 1980; Larson et al. 1980; Robin et al. 1959; Utell et al. 1989), but quantitative data are unavailable.

2.3.4.3 Dermal Exposure

Data regarding excretion of ammonia taken in by dermal exposure were not located in the available literature.

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2.3.4.4 Other Routes of Exposure

Data are available on exposure of humans and dogs to ammonium salts by intravenous injection. Excretion of isotope after ^{15}N -ammonium lactate injection in three human subjects yielded 5-7% of isotope excreted as urinary ammonia in the first 6 hours post-exposure, and another 2% within 3 days. Approximately 6% of the isotope was excreted as urea in urine in the first 6 hours. An average of approximately 60% of the dose of label was excreted in urine within 3 days. These data are considerably different from that resulting from oral loading (as described in Section 2.3.4.2). Intravenous loading led to decreased labeling of urinary urea and grossly increased labeling of urinary ammonia; the differences are attributed by the authors to a "first pass" effect from oral loading (Gay et al. 1969). The hepatic transformation of ammonium to urea is so efficient that relatively little unconverted ammonium salt is released to the general circulation.

Intravenous exposure of seven dogs to 107 mg/kg ammonium acetate led to amounts ranging from 0.044-0.073 mg ammonia excreted in expired air. No measurable amount of ammonia was present in expired air during the pre-exposure control period (Robin et al. 1959).

2.4 RELEVANCE TO PUBLIC HEALTH

The most important injurious effects of ammonia on humans are due to its irritative and corrosive properties. Following exposures to ammonia vapors, effects may be limited to irritation of the eyes and respiratory tract, but severe exposures can cause burns of the eyes, skin, and respiratory tract. Airway blockage and respiratory insufficiency can be lethal outcomes of exposure to anhydrous ammonia or concentrated aerosols. Ingestion of concentrated ammonia solutions can produce severe burns and hemorrhage of the upper gastrointestinal tract. As can be expected with extensive skin burns or injury to the respiratory or gastrointestinal tracts, secondary effects often complicate the clinical picture. These include infections and renal failure. Effects that have been observed in humans exposed to ammonia vapors and aerosols have also been observed in animals. Hepatic and renal effects have been reported in animals and humans; however, ammonia does not appear to be a primary liver or kidney toxicant.

Death. Human deaths have resulted from sudden, accidental, massive exposures to anhydrous ammonia and from ingestion of concentrated ammonia solutions. In cases of inhalation exposure, cause of death has been attributed to blocked airways, respiratory failure, bronchopneumonia, and/or renal failure. Airway blockage is most likely to occur in the upper respiratory tract (including laryngeal edema), the first tissues exposed to inhaled ammonia. It is due to fluid engorgement and edema, a response to the irritant and corrosive effect of ammonia on living tissues. Mucous membranes secrete profusely over the irritated surface and blood vessels in

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the exposed tissues dilate, causing swelling. Severe irritation causes plasma to exude from vascular walls into the respiratory passages and spaces and block them, or produce swelling and separation of tissues that leads to their death (Henderson and Haggard 1927). When these effects occur in the lungs, respiratory failure results. Necrosis resulting from the inflammatory response to exposure allows invasion of pathogenic microorganisms, and subsequent infection. In cases of oral exposure, deaths have been attributed to renal failure; however, this may be secondary to extensive gastrointestinal injury.

Systemic Effects. There are no recognized primary systemic effects from exposure to ammonia gas or ammonia solutions, probably due to limited absorption and rapid metabolic disposition. There are serious secondary systemic effects from the topical injuries that result from severe skin, eye, and gastrointestinal damage. In humans, ammonia vapor is irritating to the eyes and respiratory tract and can be corrosive when high concentrations are inhaled. Burns and related lesions and edema of the respiratory tract can lead to bronchopneumonia or secondary respiratory infections. The extent of damage increases with exposure to greater amounts. Some of the ammonia that comes in contact with the eyes reacts to form a soap. Some enters deeper layers of the eye and, in sufficient quantities, causes swelling within minutes of exposure. Ingestion of highly concentrated solutions of ammonia results in similar burns and lesions to the gastrointestinal tract and secondary complications that, at least in one case included renal failure (Klein et al. 1985). In spite of the potential toxicity of ammonia, chronic occupational exposure to low levels of airborne ammonia had no effect on pulmonary function or odor sensitivity threshold.

The irritative and corrosive properties of inhaled and ingested ammonia have been substantiated in animal studies. Mild hepatic effects and renal lesions have been reported in animals and humans, but only at near lethal concentrations. Thus, these organs do not appear to be important primary targets for inhaled ammonia.

Ingestion of lethal doses of ammonium compounds in animal studies has produced serious respiratory effects including increased rate and depth of respiration, pulmonary edema, and death by respiratory failure (Koenig and Koenig 1949). Repeated oral exposure to high doses of ammonium acidifying salts results in metabolic acidosis and secondary effects on bone and electrolyte metabolism. At the extreme, this can lead to substantial demineralization of bone and a rise in serum calcium levels. Prolonged exposures result in mild renal injury. Ammonium salts have been used extensively in humans as acidifying agents. Although renal disease has not been reported to result from such treatments, acidosis and related secondary electrolyte and bone alterations can be anticipated with prolonged oral exposure to ammonium salts or, in fact, any acidifying agent.

Other systemic effects that have been observed in animals exposed to ammonia include effects on the adrenal gland and weight loss. A study by

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Noda and Chikamori (1976) tested the relative effects of ammonium chloride and sodium chloride in diets on food intake among rats with and without bilateral lesions of the prepyriform cortex of the brain. Unlike rats with intact brains, those with lesions did not discriminate against food containing 3% ammonium chloride. Ammonium chloride injected unilaterally into intact prepyriform cortical areas reduced food intake to a greater extent than did injection of sodium chloride. Injection of the same concentration of ammonium chloride into other parts of the brain had less effect on food intake than that injected into the prepyriform cortex. These results support the thought that ammonium ions depress the appetite and that their effect is exerted by way of the prepyriform cortex.

Immunological Effects. Secondary infection has been observed in humans that have received severe burns from exposure to highly concentrated aerosols of ammonia (Sobonya 1977; Taplin et al. 1976). It is not known if this represents a primary effect on the immune system in humans. Necrosis of exposed tissues facilitates invasion by pathogenic microorganisms. Results of animal studies have shown that exposure to high concentrations of ammonia vapor can depress the immune response (Richards et al. 1978a; Targowski et al. 1984). Targowski et al. (1984) noted a significantly decreased delayed type of dermal response to tuberculin challenge among guinea pigs that had been exposed to ammonia vapor. From examination of the mitogenic and antigenic responses of lymphocytes and of the bactericidal and phagocytic activities of alveolar macrophages it has been suggested that ammonia inhibits the release of lymphokines and the mediation of specific inflammatory reactions, and that this inhibition is perhaps due to alterations at the cell membrane level. It is not known, however, to what extent inhaled ammonia can reach alveolar macrophages in vivo.

Neurological Effects. Case reports of accident victims exposed to highly concentrated aerosols of ammonia describe blurred vision, diffuse nonspecific encephalopathy, loss of consciousness, and decreased deep tendon reflexes (Hatton et al. 1979; White 1971). However, these symptoms are coincident with extensive and severe dermal and respiratory burns and respiratory insufficiency brought on by airway blockade, and may represent neurological effects secondary to anoxia. Administration of ammonium acetate subcutaneously in mice decreases spontaneous motor activity and impairs muscular coordination (Kuta et al. 1984). Furthermore, ammonium acetate antagonizes amphetamine-induced increased movement in mice, inhibits catecholamine release from isolated bovine adrenal glands, and potentiates morphine analgesia (Kuta et al. 1984). Several mechanisms could explain the neurological effects of ammonium, including changes in intracellular pH (Thomas 1974), shifts in electrolytes between intracellular and extracellular compartments (Benjamin et al. 1978), depression of inhibitory mechanisms in the brain (Lux et al. 1970; Raabe and Gumnit 1975), decreased available energy in the brain (Schenker et al. 1967; Walker and Schenker 1970), and alterations in neurotransmitter levels (Koyuncuoglu et al. 1978). Multiple biochemical effects from ammonium may explain the observed neurological impairment (Braganca et al. 1953; Hawkins et al. 1973; Nakazawa

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and Quastel 1968; Warren and Schenker 1964). It is not clear if the neurologic sequelae of experimental hyperammonemia have any relevance to inhalation or oral exposures of humans, following which hyperammonemia has not been demonstrated. However, it may be relevant to certain disease states in which endogenous ammonia metabolism is disrupted, e.g., chronic liver failure.

Developmental Effects. No information was located regarding developmental effects of ammonia in humans or animals.

Reproductive Effects. No information was located regarding the reproductive effects of ammonia in humans or animals.

Genotoxic Effects. Tests of ammonia's mutagenicity consist of studies in Escherichia coli, chick fibroblast cells, and Drosophila melanogaster (Table 2-4). Demerec et al. (1951) noted positive effects in a reverse mutation test in E. coli, but only in treatments using toxic levels of ammonia (98% lethality). Lobasov and Smirnov (1934) found slight mutagenic activity in Drosophila, but once again, survival after treatment was less than 2%. Auerbach and Robson (1947) tested Lobasov and Smirnov's results and noted 0.5% sex-linked lethals. The authors concluded that, although their data did not support the earlier study's findings, it is possible that ammonia has a very slight mutagenic action. In their data presentation, however, they report their findings as negative, qualifying it as doubtful and probably negative.

In vitro tests of chick fibroblast cells showed that buffered ammonia-ammonium chloride solutions can induce clumping of chromosomes, inhibit spindle formation and result in polyploidy (Rosenfeld 1932). Visek et al. (1972) noted reduced cell division in mouse fibroblasts cultured in media to which ammonia and ammonium chloride were added. The effect was noted in cultures irrespective of pH. Decreased rate of DNA synthesis was noted in mouse mucosal cells in the ileum and colon when serum ammonia levels were significantly elevated over normal levels; these elevated levels were induced by intraperitoneal injection of urease or infusion of ammonium chloride (Zimber and Visek 1972a).

Iwaoka et al. (1981), responding to controversy regarding mutagenicity in fried hamburgers, found that extraction of organic ingredients from fried hamburger and refrigerated biscuit products with ammonium hydroxide or ammonium sulfate increased mutagenic activities in Salmonella typhimurium T98 and TA1538 Ames' microsomal systems, while negative results were obtained from extraction with sodium sulfate. The mode of action is unclear: ammonium salts may in some way affect the mutagenic activities of some agents, or they may simply be more efficient extractors of mutagenic components from these foods.

Cancer. Carcinogenic potential of ammonia has not been established in humans or animals. One case report was found of a white male who developed

TABLE 2-4. Genotoxicity of Ammonia and Ammonium Compounds In Vitro and In Vivo

End Point	Form	Species (test system)	Result		Reference
			With Activation	Without Activation	
<u>In vitro:</u>					
Reverse mutation	NH ₃	<u>Escherichia coli</u>	NT	+ (at toxic levels)	Demerec et al. 1951
Chromosomal aberrations	NH ₄ Cl+NH ₄ OH buffer	Chick fibroblasts	NT	+	Rosenfeld 1932
Reduced cell division	NH ₃ +NH ₄ Cl	Mouse fibroblasts	NT	+	Visek et al. 1972
		Mouse fibroblasts (3T3)	NT	+	Capuco 1977
DNA repair inhibition	NH ₄ Cl	Mouse fibroblasts	NT	+	Capuco 1977
<u>In vivo:</u>					
Mutagenic lethality	NH ₃	<u>Drosophila melanogaster</u>	+	NT	Lobasov and Smirnov 1934
Sex-linked recessive lethal mutations	NH ₃	<u>D. melanogaster</u>	- (doubtful, probably negative)	NT	Auerbach and Robson 1947
Dominant lethality	NH ₃	<u>D. melanogaster</u>	-	NT	Auerbach and Robson 1947
Decreased rate of DNA synthesis	NH ₄ Cl	Mouse ileal and colonic mucosa cells	NT	+	Zimber and Visek 1972a

+ = positive result.

- = negative result.

NH₃ = ammonia.NH₄Cl = ammonium chloride.NH₄OH = ammonium hydroxide.

NT = not tested.

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epidermal carcinoma of the nasal septum 6 months after being badly burned by accidental contact with a refrigeration ammonia-oil mixture (Shimkin et al. 1954). It is unclear whether ammonia was, itself, implicated in the development of this cancer. No other such reports were located, although many cases of contact with ammonia from spills have been followed for more than 6 months after exposure. Two studies in mice [Uzvolgyi and Bojan (1985) with ammonia; Toth (1972) with ammonium hydroxide] failed to demonstrate carcinogenicity.

Colorectal cancer incidence may be influenced by ammonia production and/or concentration within the gut. Ammonia is more toxic to normal cells than to transformed cells and, in that way, selectively harms healthy tissue. Although it is not known to transform cells per se, cancer and polyp incidence are highest in areas of the colon having highest ammonia concentrations (Cummings et al. 1981; Tannenbaum and Young 1980; Visek 1978). Although very little exogenous ammonia reaches the colon, it is conceivable that ammonium compounds ingested in large doses over long periods of time could enhance the incidence of colorectal cancer. It should be noted, however, that due to the slow transport capabilities of the colon, other potential carcinogens may also be present for extended periods of time,

Some data suggest that ammonia may act as a co-carcinogen with certain other substances. Mice developed lung tumors after gavage administration of ammonia dissolved in water and diethyl pyrocarbonate, while neither compound alone produced tumors (Uzvolgyi and Bojan 1980, 1985). The authors suggested that ammonia and diethyl pyrophosphate reacted in vivo to form the carcinogen, urethane, which produced a 100% incidence of lung tumors in the mice. Increased incidence of colorectal tumors was observed in mice that received intrarectal doses of ammonium acetate and N-methyl-N'-nitrosoguanidine (MNNG) compared to control mice that received MNNG and distilled water (Clinton et al. 1988). The involvement of acetate in the apparent tumor promotion by ammonium acetate was not ruled out.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC, 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary

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levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to ammonia are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by ammonia are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Ammonia

There are no known specific biomarkers of exposure for ammonia. Identification of biomarkers of exposure to ammonia is confounded because large amounts of ammonia are produced endogenously. Pharmacokinetic studies reveal that after inhalation exposure to low levels of ammonia, BUN, nonprotein nitrogen, urinary-urea, and urinary-ammonia levels do not change. Exposure to common occupational limits of ammonia in air (26 ppm) yield increased blood-ammonia levels only 10% above fasting levels. In one human study, oral ingestion of ammonium chloride tablets yielded only a transient increase in blood-ammonia above fasting levels in 11 out of 20 subjects tested; no increase was observed in the remaining 9 subjects.

Effect biomarkers of ammonia exposure are limited to site-of-contact tissue injuries. Upon inhalation exposure, distribution of ammonia is usually limited to the respiratory tract and involves irritation and, at higher concentrations, pulmonary edema and necrosis. Oral exposure to high doses of ammonium chloride has produced pulmonary edema in animals. Dermal exposure to ammonia causes skin and eye irritation and, at higher

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concentrations, necrosis. The severity of injuries by all routes of exposure are dose-related. Unfortunately, these effect biomarkers are not specific for ammonia and can be caused by a variety of caustic substances.

2.5.2 Biomarkers Used to Characterize Effects Caused by Ammonia

The tissues and organs most sensitive to ammonia exposure are mainly dependent on route of exposure. After inhalation exposure, which can involve a significant dermal exposure, the skin and eyes and the respiratory tract, including the lungs, are most sensitive. Direct dermal exposure produces dose-related effects from irritation to necrosis. Ingestion of ammonium hydroxide has resulted in oral, pharyngeal, and esophageal lesions. The tissue and organ injuries produced by ammonia, however, are of limited value as biomarkers to characterize the effects caused by ammonia because many other caustic chemicals can produce similar injuries.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Exposure to substances that would increase the pH of exposed tissues could be expected to enhance the alkalotic effects of ammonia, and vice versa. Agents acting to elevate the intestinal-tract pH would increase its local irritant effect, and would promote its absorption, as well (Castell and Moore 1971).

Co-administration of ammonia and diethyl pyrocarbonate induced lung tumors in mice, while neither agent administered intragastrically and separately was carcinogenic; this effect is believed to be a result of a compound, urethane (a known carcinogen), produced by their interaction (Uzvolgyi and Bojan 1980, 1985). Mice given intrarectal doses of MNNG and ammonium acetate had a higher incidence of tumors than did controls that were administered distilled water in place of ammonium acetate (Clinton et al. 1988). The role of acetate was not ruled out. Ammonia acted synergistically with potassium ions on pyruvate kinase, a known Ehrlich ascites tumor enzyme (Olavarria et al. 1986).

Some compounds play a synergistic role with ammonia in producing hepatic coma. Simultaneous injection of an ammonium salt and a fatty acid produced coma at lower plasma levels than did injection of either compound separately. Inhalation of methanethiol or injection with sodium octanoate blocked metabolism of an injected dose of ammonium acetate and led to elevated blood ammonia levels (Zieve et al. 1974).

Data regarding exposure to mixtures of atmospheric contaminants indicate that, contrary to what might be expected, increased carbon dioxide concentration (up to 5% in air) does not alter the hyperventilatory rate induced by hyperammonemia (Herrera and Kazemi 1980). Ammonia in expired air neutralizes inhaled acid aerosols (Larson et al. 1980; Loscutoff 1979; Utell et al. 1989).

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Other substances to which people have been exposed have been shown to alter the toxic effects of ammonia. Methionine sulfoximine, administered by intraperitoneal injection, suppressed the tonic convulsions produced by intravenous injection of ammonium chloride in mice (Hindfelt and Plum 1975; Warren and Schenker 1964). Intraperitoneal injection of alpha-methylglutamic acid also exerts a protective effect against hyperammonemia in rats (Lamar 1970). Nicotinoxyhydroxamic acid and neomycin administered orally reduce blood ammonia levels and increase excretion of urea by treated rats (Harada et al. 1985). Ethanol exerted a protective effect on acute ammonia intoxication in mice (O'Connor et al. 1982), although ethanol was reported to increase ammonia concentrations in body tissues of treated rats (Mohanachari et al. 1984).

Sodium benzoate decreased urea production in ammonia challenged rats (Maswoswe et al. 1986) and hyperammonemic mice (O'Connor et al. 1987). Valproate, a widely used antiepileptic drug, has a hyperammonemic effect (Ferrier et al. 1988) and may therefore predispose to ammonia intoxication. Ammonia interferes with the metabolism of pent-4-enoic acid in cultured rat hepatocytes and may dramatically potentiate its toxicity (Coude and Grimber 1984).

2.7 POPULATIONS THAT ARE USUALLY SUSCEPTIBLE

Persons who suffer from severe advanced liver or kidney pathology may be susceptible to ammonia intoxication, as it is chiefly by the actions of these organs that ammonia is biotransformed and excreted. In these individuals, the levels produced endogenously are sufficient to produce toxicity. Levels that are likely to be encountered in the environment, with the exception of those resulting from high-level accidental exposures, are insignificant, due to the low absorption rate, in comparison with levels produced within the body (WHO 1986).

Since ammonia is a respiratory tract irritant, persons who are hyperreactive to other respiratory irritants, or who are asthmatic, would be expected to be more susceptible to ammonia inhalation effects. The results of an epidemiological study of a group of workers chronically exposed to airborne ammonia indicate that ammonia inhalation can exacerbate existing symptoms including cough, wheeze, nasal complaints, eye irritation, throat discomfort, and skin irritation.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ammonia is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to

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determine the health effects (and techniques for developing methods to determine such health effects) of ammonia.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of Ammonia

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to ammonia are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of ammonia. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Information regarding health effects of ammonia in humans consists largely of case reports of fatalities or illnesses following massive inhalation and/or dermal exposures resulting from accidental explosions or leakages. A few controlled studies have been conducted on inhalation and oral exposure effects. Health effects of ammonia in animals have been investigated in numerous inhalation studies, and a few oral and dermal exposure studies. Clearly, ammonia is an acutely toxic chemical in high concentrations, but it is also one which is readily detected in air, water, and upon skin and eye contact. As indicated in Figure 2-5, available data address these concerns, both in humans and animals. The data indicate that airway blockage, edema, burns and lesions of tissues directly exposed to ammonia are the most prominent ammonia-related effects. Secondary effects include liver and kidney damage, along with decreased resistance to disease.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Data is available in humans to identify the primary organs and tissues sensitive to ammonia exposure by all routes. Acute-duration exposure by all routes yields dose-related site-of-contact lesions primarily of the skin, eyes, and respiratory tract, including the lungs. Organ-specific toxicity which depends on absorption and systemic distribution does not appear to be important, although some animal studies indicate that liver and/or kidney toxicity may result from very high concentrations of ammonia. Studies in animals provide strong support for the data in humans. Data for acute-duration exposure were sufficient to yield an acute inhalation MRL based on nose and throat irritation in humans. An acute-duration oral MRL was not derived because a threshold effect level could not be identified; the concentration at which death occurred in

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	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation	●	●	●	●	●					
Oral	●	●								
Dermal	●	●	●							

HUMAN

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation	●	●	●		●	●		●		
Oral	●	●	●						●	●
Dermal	●	●								

ANIMAL

● Existing Studies

FIGURE 2-5. Existing Information on Health Effects of Ammonia and Ammonium Compounds

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animals was lower than the highest NOAEL identified for other endpoints. Additional data for acute-duration exposure do not seem warranted at this time.

Intermediate-Duration Exposure. Data from intermediate-duration inhalation exposure are sufficient to identify the respiratory tract and skin of humans and animals as the primary target organs of ammonia toxicity. Although an MRL for intermediate-duration oral exposure has been derived, the available studies have not sufficiently identified target organs in humans or animals. Most of the studies are old and methods for quantifying exposure and effects may not have been adequate by present-day standards. Pharmacokinetic data are not available to aid in the assessment of intermediate-duration oral exposure. Only one intermediate-duration dermal exposure study was located and reported transitory eye irritation after exposure to low concentrations of ammonia was observed in humans. The paucity of data from intermediate-duration oral and dermal studies underscores the importance of further study both to help identify potential target organs of toxicity and because there are populations surrounding hazardous waste sites that might be exposed to ammonia for intermediate durations.

Chronic-Duration Exposure and Cancer. The available chronic-duration exposure data are insufficient to identify target organs of toxicity for any route of exposure. No studies of chronic-duration are available for dermal exposure. A single human study of chronic-duration inhalation exposure was located but no respiratory effects attributable to ammonia were observed. A chronic inhalation MRL was derived from the highest NOAEL value from this occupational study because the respiratory system is the most sensitive system for inhalation exposure to ammonia for acute and intermediate durations. A single chronic-duration oral exposure study was located that identified a LOAEL for musculo/skeletal effects and decreased body weight in the rat. The available data were not sufficient for an oral MEL derivation because target organs were not identified. Pharmacokinetic data are not available to aid in the assessment of potential toxicity after chronicduration exposure. Because there are populations surrounding hazardous waste sites that might be chronically exposed to ammonia it would be valuable to investigate chronic-duration exposures by all routes to identify target organs and dose-effect relationships.

There is no evidence to support the potential for carcinogenicity of ammonia in humans or animals, although, lifetime exposure studies have not been conducted for inhalation or dermal exposure. A two-year oral exposure study in mice revealed no evidence for carcinogenicity nor an effect on the spontaneous rate of breast tumors. Pharmacokinetic data are not available to aid in the assessment of carcinogenicity. Because there are populations surrounding hazardous waste sites that might be exposed to ammonia for their lifetimes it would be valuable to conduct lifetime inhalation and dermal exposure studies to reduce the uncertainty associated with carcinogenic potential.

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Genotoxicity. No information was located regarding the genotoxicity of ammonia in humans. In vivo animal data are limited to studies in Drosophila melanogaster which resulted in a positive response for mutagenic lethality but negative responses for sex-linked recessive lethal mutations and dominant lethality. These are old studies, however, and may not meet present-day standards of technology. In vitro studies revealed positive responses for genotoxicity in Escherichia coli, chick and mouse fibroblasts. Again, however, these are mainly old studies, and, at least in one case, required toxic levels of ammonia to produce effects. Based on its structure, ammonia is not expected to be highly genotoxic. It would be valuable to further assess the genotoxicity of ammonia with mutagenicity assays in Salmonella typhimurium followed by in vitro and/or in vivo tests for chromosomal aberrations in mammalian systems if positive responses are obtained.

Reproductive Toxicity. No information was located regarding reproductive effects of ammonia in humans or animals. Pharmacokinetic data are not available to aid in the assessment of the potential for reproductive toxicity in humans or animals. The high levels of ammonia produced endogenously in animals, however, suggest that reproductive organs and tissues are not a likely target of ammonia toxicity. Further study, in the absence of more definitive acute-, intermediate-, and chronic-duration toxicity studies, does not seem warranted at this time.

Developmental Toxicity. No information was located regarding developmental effects of ammonia in humans or animals. Pharmacokinetic data are not available to aid in the assessment of the potential for developmental toxicity in humans or animals. The high levels of ammonia produced endogenously in animals, however, suggest that developmental effects are unlikely to occur after exposure to ammonia. Further study, in the absence of more definitive acute-, intermediate-, and chronic-duration toxicity studies, does not seem warranted at this time.

Immunotoxicity. Secondary infection has been observed in humans that have received severe burns from exposure to highly concentrated aerosols of ammonia. It is not known if this represents a primary effect on the immune system in humans since necrosis of exposed tissues facilitates infection by pathogenic organisms. Animal studies have shown that exposure to ammonia may inhibit the immune response. There is no reason to suspect that immune system effects could be route- or species-specific. It would be valuable to assess the potential for immunotoxicity of ammonia with a battery of immune function tests.

Neurotoxicity. Neurological effects have been observed in humans who received extensive and serious burns from exposure to anhydrous ammonia. These effects may be secondary to trauma, rather than direct effects of ammonia on the central nervous system. Animal studies have not revealed overt neurological impairment following sublethal inhalation or oral

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exposures to ammonia; however, sensitive indicators of neurologic impairment have not been examined in animal models of ammonia exposure. In view of the known actions of hyperammonemia, further examination of the neurologic effects of repeated inhalation and oral exposure in animals might provide a basis for evaluating the potential for neurologic effects of such exposures in humans.

Epidemiological and Human Dosimetry Studies. A chronic epidemiological study found no adverse effects of low level ammonia exposure on pulmonary function or odor sensitivity in humans. Several human dosimetry studies have established taste and odor threshold levels, irritation thresholds, and tolerable exposure levels. Based on these studies, it is clear that the presence of ammonia can be detected by most persons at levels well below those causing serious or lasting effects. These studies are limited because most graded responses are subjective and dose-effect analysis cannot be conducted at concentrations that produce obvious injury. There are no studies which identify a subpopulation that is particularly sensitive to ammonia exposure. Epidemiological studies of humans occupationally exposed or residing for long periods of time near hazardous waste sites where ammonia is stored would provide valuable information that is not found in human dosimetry studies or in clinical case histories.

Biomarkers of Exposure and Effect. There are no known specific biomarkers of exposure for ammonia in humans or animals. Furthermore, no evidence for alterations in clinical indices of body ammonia or nitrogen levels after exposure to exogenous ammonia have been reported. It does not seem useful at this time to develop biomarkers of exposure for ammonia because, after exposure to low levels, ammonia is either rapidly cleared from the body or metabolized to compounds found endogenously at appreciable levels. Exposure to high concentrations is immediately and overtly toxic which eliminates the need for a more subtle biomarker.

There are no known specific biomarkers of effect for ammonia in humans or animals. Lesions produced by exposure to high concentrations of ammonia are similar to those produced by other caustic substances. Until more definitive studies have been completed that identify target organs and dose-effect relationships after acute, intermediate, and chronic duration, there is little value in developing biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. Measurement of ammonia absorption is complicated by the appreciable levels of endogenously produced ammonia. It appears, however, that inhalation exposure to low levels of ammonia results in a small amount of absorption. Most of the inhaled ammonia is retained in the tissues of the upper respiratory tract, As the ammonia concentration increases, the ability of the upper respiratory tract to retain ammonia is saturated, and a larger percentage is absorbed into the blood stream. Absorption into the systemic circulation after oral exposure is limited. Ammonia absorbed from the gastrointestinal tract

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travels via the hepatic portal vein directly to the liver where, in healthy individuals, most of it is converted to urea and glutamine. Although it has not been extensively studied, dermal absorption of ammonia does not occur to a great extent; WHO (1986) concluded that systemic effects from skin and eye exposure to ammonia are not quantitatively important. Data are not available to assess the distribution of ammonia in humans or animals. Studies on endogenously produced ammonia, however, indicate that it is distributed to most of the organs and tissues of the body. Extensive work has been completed on the metabolism of ammonia and its participation in the glutamine cycle and the urea cycle. Data regarding excretion are limited but it is known that ammonia inhaled at low levels is excreted primarily unchanged in the expired breath; ammonia absorbed from the gastrointestinal tract is excreted primarily in the urine as urea and urinary ammonia compounds. No information regarding excretion after dermal exposure was located. Until more definitive studies have been completed that identify target organs and dose-effect relationships after acute, intermediate, and chronic duration there is little value in more extensive pharmacokinetic studies.

Comparative Toxicokinetics. Available data indicate that ammonia has similar targets of toxicity in humans and animals. Ammonia is most hazardous as a site-of-contact toxicant; therefore, the respiratory system is most vulnerable after inhalation exposure, the gastrointestinal tract is most vulnerable after oral exposure, and the skin and eyes are most vulnerable after dermal/ocular exposure. Limited human and animal data are available for toxicokinetics; however, these data indicate that humans and animals are probably very similar regarding the toxicokinetic disposition of ammonia. Furthermore, it is reasonable to expect, especially given the biochemical importance of ammonia, that humans and animals would handle this compound similarly.

2.8.3 On-going Studies

Studies are being conducted by the National Institute of Diabetes and Digestive and Kidney Diseases on renal ammonia genesis, amino acid metabolism and gluconeogenesis in various acid-base states in an effort to deepen understanding of renal ammonia genesis in response to perturbations of hydrogen ion homeostasis. These studies will use isolated renal cortical mitochondria and also intact rat renal tubules in the presence and absence of metabolic modulators and/or inhibitors. A study of colonic transport of electrolytes, organic anions and ammonia is in progress, sponsored by the Veterans Administration Research and Development (Federal Research in Progress 1988).

Pathogenesis of hepatic coma is the focus of several current studies. Most of these focus on the brain and ammonia's interference with cerebral energy metabolism. One study, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, is investigating the biochemical effects on cultures of neurons and astrocytes of acute and chronic exposure

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to excess ammonia and Beta-methyleneaspartate (BetaMA), a known inhibitor of aspartate aminotransferase; it is possible that astrocytes are more susceptible to ammonia-induced metabolic impairment than are neurons with respect to interference with the tricarboxylic acid cycle. Another study, sponsored by the National Institute of Neurological and Communicative Disorders and Stroke, is focused on neurotoxicity of ammonia and shortchain fatty acids, and is testing hypotheses that these compounds interfere with the tricarboxylic acid cycle activity and also alter the structure and function of the neuronal plasma membrane. Both of these studies are being carried out at Cornell University Medical Center, New York, New York.

Another study, described only as examining neuronal effects of ammonia, is in progress at the Veterans Administration, Research and Development, in Washington, DC (Federal Research in Progress 1988).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of ammonia are presented in Table 3-1. These data are for ammonia in its pure gaseous state, i.e., anhydrous ammonia. Ammonia is also available as an aqueous solution, the most common commercial formulation being 28-30% NH_3 (Weast 1988). At this concentration, ammonia forms a nearly saturated solution in water. Data on ammonia in aqueous solution, ammonium hydroxide, are also included in Table 3-1 where appropriate.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Ammonium hydroxide is a weak base which is partially ionized in water according to the equilibrium:



The dissociation constant, K_b , is 1.774×10^{-5} at 25°C ($\text{p}K_b$ is 4.751) and increases slightly with increasing temperature (Weast 1988). At pH 9.25 half of the ammonia will be un-ionized (NH_3) and half will be ionized (NH_4^+). At pH 8.25 and 7.25, 90, and 99% of the ammonia will be ionized, respectively. Therefore, over most of the environmentally significant range of pHs, ammonia will be largely ionized; the fraction of un-ionized ammonia will become increasingly more important at pHs above 7. As a result, many physical and chemical properties will be a function of pH. For example, the solubility of ammonia in water will increase with decreasing pH. The volatility of ammonia increases with increasing pH; therefore, it volatilizes freely from solution at high pH values. Ammonium salts such as chloride, nitrate, and sulfate are strongly dissociated and very soluble in water (Weast 1988); Therefore shifts in the ionization will not normally result in the formation of precipitates.

The physical and chemical properties of ammonia are presented in Table 3-2. Also included are some chemical and physical properties of ammonia in solution. Ammonia in solution is widely available, and it is commonly referred to as ammonium hydroxide or spirit of hartshorn (Windholz 1983).

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Ammonia

	Value	Reference
Chemical name	Ammonia	
Synonyms	Anhydrous ammonia	Windholz 1983
Trade names	No data	
Chemical formula	NH ₃	
Chemical structure	$\begin{array}{c} \text{H}-\text{N}-\text{H} \\ \\ \text{H} \end{array}$	
Identification numbers:		
CAS Registry	7664-41-7	CAS 1988
NIOSH RTECS	BO0875000	RTECS 1988
aqueous solution	BQ9625000	
EPA Hazardous Waste	No data	
OHM-TADS	7216584	OHM-TADS 1988
DOT/UN/NA/IMCO Shipping	UN 1005	HSDB 1988
solution >44%	UN 2073	
solution >50%	UN 2672	
HSDB	162	HSDB 1988
NCI	ND	

CAS = Chemical Abstracts Service

DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code

EPA = Environmental Protection Agency

HSDB = Hazardous Substances Data Bank

NCI = National Cancer Institute

NIOSH = National Institute for Occupational Safety and Health

OHM-TADS = Oil and Hazardous Materials/Technical Assistance Data System

RTECS = Registry of Toxic Effects of Chemical Substances

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of Ammonia

Property	Value	Reference
Molecular weight	17.03	LeBlanc et al. 1978
Color	Colorless	LeBlanc et al. 1978
Physical state	Gas at room temperature	LeBlanc et al. 1978
Melting point	-77.7°C	LeBlanc et al. 1978
Boiling point	-33.35°C	LeBlanc et al. 1978
Density:		
Gas	0.7710 g/L	Weast 1988
Aqueous solution (28%)	0.89801 (20°C) g/L	Windholz 1983
Liquid	0.6818 g/L (-33.35°C, 1 atm)	Windholz 1983
Vapor density	0.5967 (air = 1)	Windholz 1983
Odor	Sharp, intensely irritating	Sax and Lewis 1987
Odor threshold:		
Water	1.5 ppm	Amoore and Hautala 1983
Air	25 ppm 48 ppm	Leonardos et al. 1969
Solubility:		
Water	42.8% (0°C); 33.1% (20°C); 34% (25°C)	LeBlanc et al. 1978
Organic solvents	Hydroscopic Soluble in alcohol, ether, organic solvents	Weast 1988; Windholz 1983
Partition coefficient:		
Log octanol/water	No data	
Log K _{oc}	No data	
Vapor pressure:		
Anhydrous NH ₃	8.5 atm (20°C)	Sax and Lewis 1987
Aqueous NH ₃ (28%)	447.0 mmHg (20°C)	EPA 1983
Henry's law constant	7.3x10 ⁻⁶ atm-m ³ /mol (pH 7, 23.4°C) ^a 1.60x10 ⁻⁵ atm-m ³ /mol (25°C) ^b 5.01x10 ⁻⁶ atm-m ³ /mol (5°C)	Ayers et al. 1985; Yoo et al. 1986; Brimblecombe and Dawson 1984
Autoignition temperature	650°C	LeBlanc et al. 1978

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2 (Continued)

Property	Value	Reference
Flammability limits in Air	16-25%	LeBlanc et al. 1978
Conversion factors		
ppm (v/v) to mg/m ³ in air (20°C)	1 ppm (v/v) = 0.708 mg/m ³	
mg/m ³ to ppm (v/v) in air (20°C)	1 mg/m ³ = 1.41 ppm (v/v)	
pH in water	11.6 (1 N) 11.1 (0.1 N) 10.6 (0.01 N)	Windholz 1983

^aUnitless constant extrapolated from cited data.

^bUnconverted value of 0.0168 kg-atm/mol was calculated from equation in citation.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Ammonia is both a natural and a man-made chemical. It is a key intermediate in the nitrogen cycle in nature, and microbial production is by far the major source of ammonia in the world. The total annual commercial production of ammonia was estimated to represent approximately 1-5% of nature's global ammonia budget (ApSimon et al. 1987; Buijsman et al. 1987; Crutzen 1983; Galbally 1985; Rosswall 1981).

The largest amount of ammonia produced in the world is thought to arise from soil. Ammonia from decomposing animal excreta probably accounts for the largest proportion of the ammonia produced, with the decay of organic materials from plants, dead animals, and the like contributing significant amounts (Crutzen 1983; Dawson 1977; Dawson and Farmer 1984; Galbally 1985; Irwin and Williams 1988).

United States annual commercial production capacity for ammonia was 17.3 million metric tons in 1988 (SRI 1988). Of the 63 plants capable of producing ammonia, 6 plants, with a combined capacity of 963,000 metric tons, were closed indefinitely (SRI 1988). Twenty-nine plants contributed greater than 100,000 tons each to the total; the three largest contributors, at greater than 1 million tons each (more than 907,000 metric tons), were Agrico, CF Industries, and Farmland Industries (CMR 1988). Unocal and W.R. Grace were also listed as major producers (C & E News 1987). In 1979, United States production of ammonia was 18 million tons (16,300,000 metric tons), 73% of capacity (EPA 1980a); for this year, 101 United States ammonia plants in 30 states were on line. Texas and Louisiana are listed as the two major producing states. These states, along with California, Iowa, and Oklahoma accounted for 70% of the total United States production in 1979.

The major method for commercial production of anhydrous ammonia is a modified Haber-Bosch process. This process was commercially developed in 1913 in Germany. The first United States plant to use this process was built in Syracuse, NY, in 1921 (Davis 1985). The basic Haber-Bosch methodology was still responsible for 98% of the industrially produced ammonia in the United States in 1979 (EPA 1980a). In this process, nitrogen (obtained from the atmosphere) and hydrogen (obtained from natural gas) are mixed together in a 1 to 3 ratio and passed over a catalyst at high pressure. The ammonia thus produced is collected by various means, and any unreacted feed gas is recirculated through the reactor.

Small amounts of ammonia are produced industrially as a by product of the coking of coal. The largest proportion of industrial ammonia production occurs in areas where natural gas is cheap and plentiful. Large pipelines stretching from Louisiana to Nebraska and Texas to Minnesota carry anhydrous ammonia from its site of production to agricultural areas where it is used as fertilizer (LeBlanc et al. 1978). These pipelines are capable of transporting 7000 tons of ammonia per day. Ammonia can also be shipped in large refrigerated, low pressure tanks (4-30 thousand tons) or smaller

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

(210 tons) pressurized tanks (Farm Chemicals Handbook 1987). Barges are often used for refrigerated shipments because of their lower cost. Ammonia can be stored in refrigerated tanks holding up to 36,000 tons for use in the ammonia market. Smaller amounts of ammonia are stored in pressurized tanks.

Domestic production has consistently met the demand, and should remain relatively constant, yet it will depend on both the amount of crop acres planted and the price of imported fertilizers.

4.2 IMPORT

Imports into the United States totaled more than 2.5 million tons (2.27 million metric tons) in 1986 (C & E News 1987). United States exports of ammonia were 500,000 tons (453,000 metric tons).

4.3 USE

The largest and most significant use of ammonia and ammonium compounds is the agricultural application of fertilizers. Ammonia and ammonium compounds used as fertilizer represent 80% of the commercially produced ammonia, with fiber and plastics, explosives, and other uses accounting for 10, 5, and 5%, respectively (C & E News, 1987). Direct uses of ammonia can be broken down into the following categories: direct application fertilizer, 27%; urea, 21%; ammonium phosphates, 14%; nitric acid, 11%; ammonium nitrate, 8%; exports, 6%; ammonium sulfate, 3%; other, 10% (CMR 1988). Most ammonium compounds and nitric acid which are produced from anhydrous ammonia are used directly in the production of fertilizers.

The small proportion of commercially produced ammonia not incorporated into fertilizers is used as a refrigerant, a corrosion inhibitor, in the purification of water supplies, and as a component of household cleaners. It is also used in the pulp and paper, metallurgy, rubber, food and beverage, textile, and leather industries. Ammonia is used in the manufacture of pharmaceuticals and explosives, and in the production of various chemical intermediates (LeBlanc et al. 1978; Sax and Lewis 1987).

4.4 DISPOSAL

Solutions of ammonia can be highly diluted with water, or alternatively, diluted with water and neutralized with HCl and then routed to the sewer system. The receiving stream should not exceed the established limits for ammonia. Limited amounts of gaseous ammonia may be discharged to the atmosphere. Federal, state, and local guidelines should be consulted before disposal.

Disposal of liquified ammonia or of large quantities of gaseous or aqueous ammonia directly into water is not desirable, because of the large amount of heat generated. This generation of heat could increase exposure

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

to personnel involved in the process. Recovery of ammonia from aqueous waste solutions is a viable option for many industries (HSDB 1988; OHM-TADS 1988).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Ammonia is a naturally-occurring compound which is a key intermediate in the nitrogen cycle. Under normal conditions, ammonia is essential for many biological processes. The commercial synthesis of ammonia is thought to contribute less than 5% to the total global ammonia budget. Because of its significance in natural cycles, ammonia has a background concentration in most environmental media. When ammonia is found at a local concentration that is higher than these background levels, it is usually a result of man's influence. Ammonia is hazardous only when exposure is to high levels. In determining the environmental fate of ammonia, several factors should be considered. Ammonia is the most abundant basic gas in the environment. An acid-base reaction between water and ammonia occurs, such that the dominant form of ammonia in water, at environmentally significant phs, is the ammonium ion. In media where water is usually present, such as soil, plants, biological tissue, and water itself, ammonia and ammonium are in dynamic equilibrium.

Ammonia is a key intermediate in the nitrogen cycle, a natural cycle which is tied to the other important biological cycles (i.e., sulfur cycle or carbon cycle). An understanding of the role of ammonia in the nitrogen cycle, at least on a generalized level, is important in determining the environmental fate of ammonia.

A simplified schematic of the microbial processes of the nitrogen cycle which involve ammonia can be found in Figure 5-1. Four processes in the nitrogen cycle performed by microorganisms to produce or transform ammonia are nitrogen fixation, nitrification, denitrification, and ammonification. As part of this cycle, nitrogen gas and oxidized forms of nitrogen are returned to the biological world. Nitrogen fixation is the process whereby atmospheric nitrogen gas is converted to ammonia; only a few species of microorganisms have the ability to fix nitrogen. Denitrification is the process whereby nitrogen oxides are reduced under anaerobic conditions to N_2 and N_2O which can escape to the atmosphere. Nitrification is the biological oxidation of ammoniacal nitrogen or other reduced forms of nitrogen to nitrate with nitrite as the intermediate. Ammonification is the conversion of organic nitrogen into inorganic ammonia.

Ammonia may be released to the atmosphere by volatilization from the following sources:

- Decaying organic matter
- Animal livestock excreta
- Fertilization of soil

5. POTENTIAL FOR HUMAN EXPOSURE

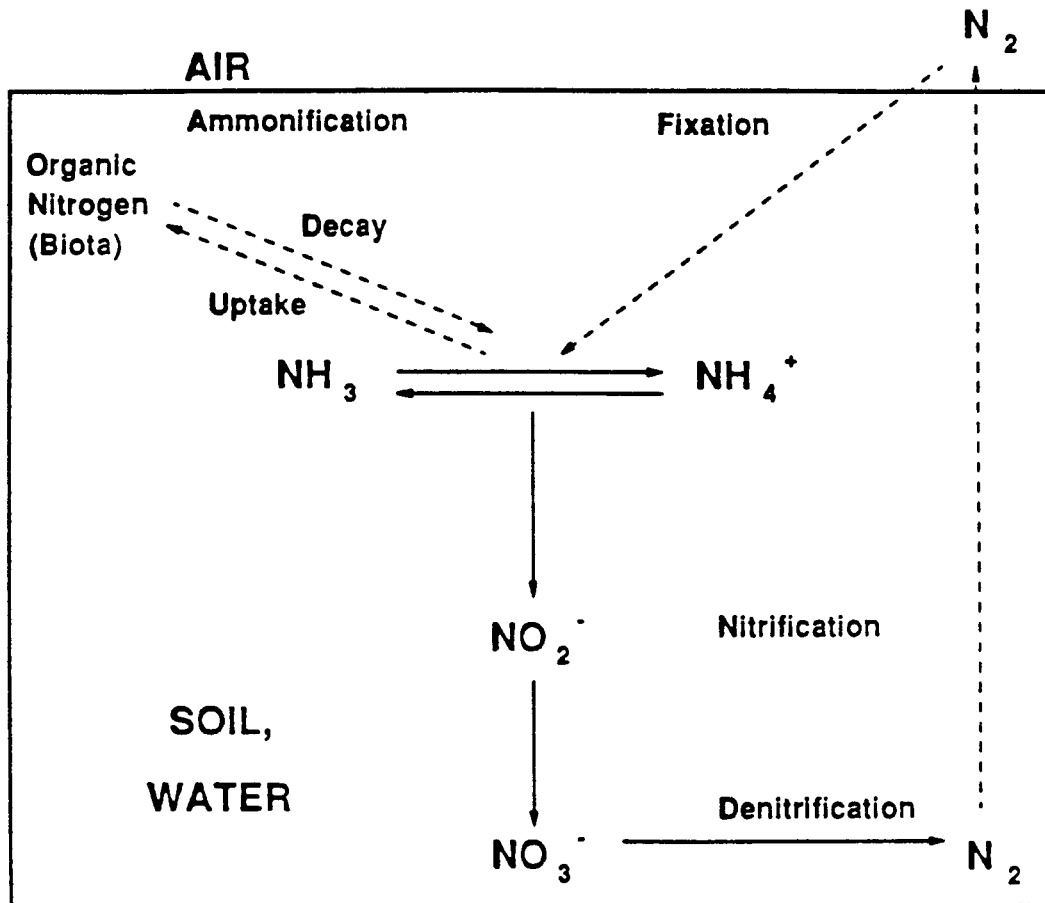


FIGURE 5-1. Simplified Schematic for the Microbial Processes of the Nitrogen Cycle

5. POTENTIAL FOR HUMAN EXPOSURE

- Venting of gas, leaks, or spills during commercial synthesis, production, or transportation
- Sewage or wastewater effluent
- Burning of coal, wood, and other natural products
- Volcanic eruptions

Ammonia may be released to water through the following:

- Effluent from sewage treatment plants
- Effluent from industrial processes
- Runoff from fertilized fields
- Runoff from areas of concentrated livestock

Ammonia may be released to soils by:

- Natural or synthetic fertilizer application
- A result of livestock excrement
- Decay of organic material from dead plants and animals
- The natural fixation of atmospheric nitrogen

In the atmosphere, ammonia can be removed by rain or snow washout. The reaction with acidic substances, such as H_2SO_4 , HCl , or HNO_3 , produced in high concentrations from anthropogenic activity produces ammonium aerosols which can then undergo dry or wet deposition. The gas phase reaction of ammonia with photochemically produced hydroxyl radicals is thought to contribute about 10% to the overall atmospheric removal process. The best estimate of the half-life of atmospheric ammonia is a few days.

In water, ammonia volatilizes to the atmosphere. This process is highly pH-dependent, and can also depend on other factors such as temperature and wind speed, and atmospheric concentration. Ammonia in water can be removed by the microbial processes of nitrification and denitrification. Nitrification yields nitrate and nitrite anions; the former species can be responsible for methemoglobinemia in human infants if the contaminated water is ingested. Adsorption of ammonia to sediment and suspended organic material may occur.

5. POTENTIAL FOR HUMAN EXPOSURE

In soil, ammonia may either volatilize to the atmosphere, adsorb to soil, or undergo microbial transformation to nitrate or nitrite anions. Uptake by plants can also be a significant fate process. Ammonia at natural concentrations in soil is not believed to have a very long half-life. If ammonia is released to soil in large concentrations, the natural processes can become overwhelmed, and the environmental fate of ammonia will become dependent upon the physical and chemical properties of ammonia, until the ammonia concentration returns to tolerable levels.

Occupational exposure to ammonia may occur in industries involved in its synthesis, formulation, transportation, and use. Occupational exposure to ammonia can occur during the use of an extensive number of cleaning products that contain ammonia. Farmers may be exposed during the application of fertilizers, and workers at cattle feedlots, poultry confinement buildings, or other industries which have a high concentration of animals may also be exposed.

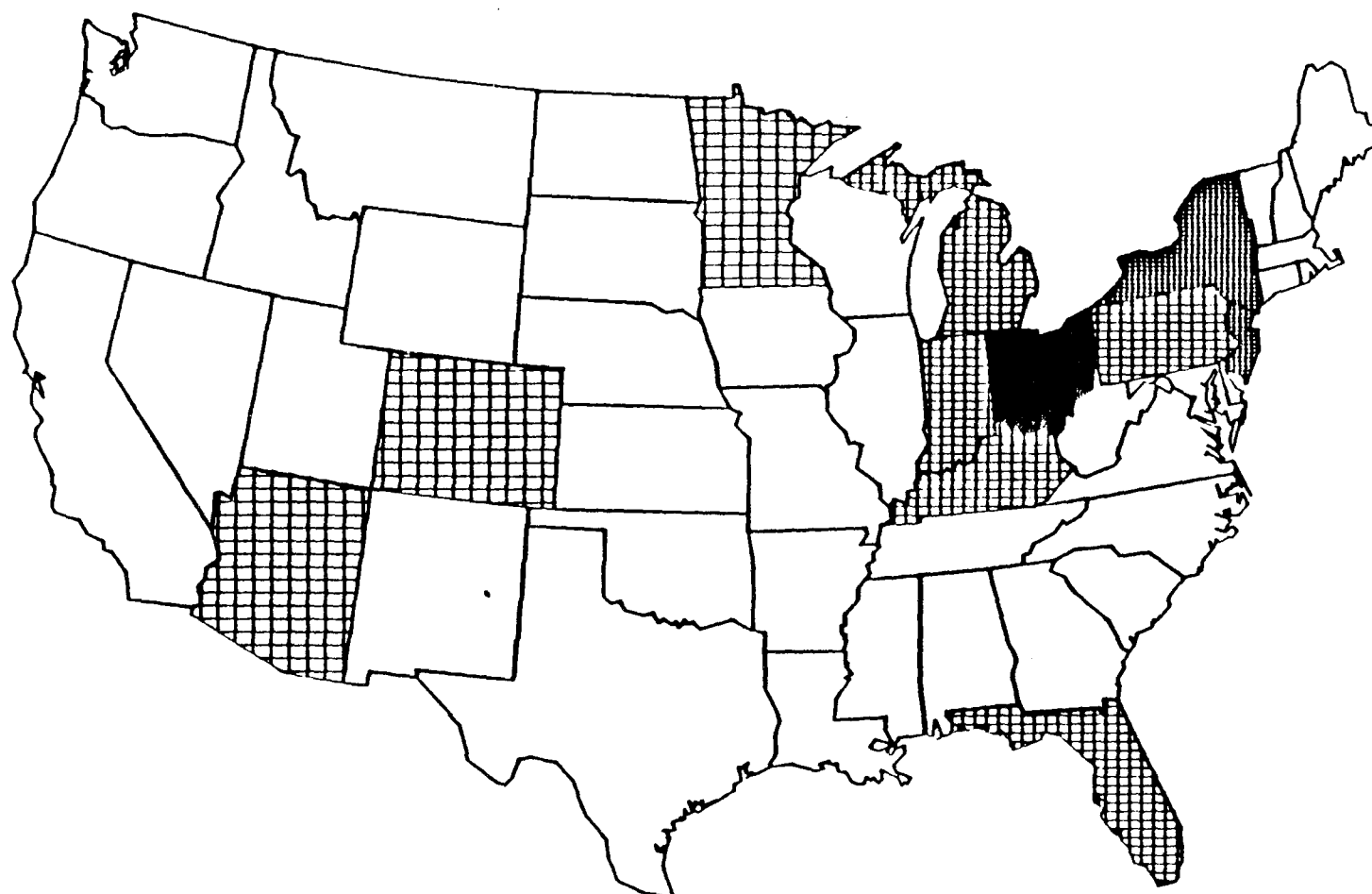
Exposure of the general population to elevated levels of ammonia is most commonly from the use of household cleaners containing ammonia. People who live near farms or who visit farms during the application of fertilizer may also be exposed. People living near cattle feedlots, poultry confinement buildings, or other areas where animal populations are concentrated can also be exposed to ammonia, in addition to other gases generated by putrefaction. Ammonia has been identified at 23 out of 1177 National Priority List (NPL) hazardous waste sites in the United States (VIEW Database 1989). The frequency of these sites within the United States can be seen in Figure 5-2.

5.2 RELEASES TO THE ENVIRONMENT

Ammonia is released to the environment as a result of the activities of both man and nature. Ammonia is a key intermediate in nature's nitrogen cycle, and as such, ammonia concentrations in nature and natural media are in dynamic equilibrium. When ammonia is found at elevated concentrations, it is usually a result of anthropogenic activity.

5.2.1 Air

Large amounts of ammonia are released to the atmosphere worldwide by domesticated farm animals (ApSimon et al. 1987; Asman and Janssen 1987; Ryden et al. 1987). Ammonia emissions due to the decay of livestock manure are a source for ammonia release in areas that have artificially high concentrations of animals, such as cattle feedlots and poultry confinement buildings (Hutchinson et al. 1982). The use of high nitrogen content feed for farm animals, and the trend toward larger feedlots, has been responsible for increased emissions in developed countries. The application of fertilizer to soil, as ammonia, ammonium compounds, or ammonia precursors (such as urea), is a well documented source of ammonia



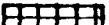



FREQUENCY  1 SITE  2 SITES  3 SITES  4 SITES

FIGURE 5-1. FREQUENCY OF SITES WITH AMMONIA CONTAMINATION

5. POTENTIAL FOR HUMAN EXPOSURE

release to the atmosphere (ApSimon et al. 1987; Beyrouthy et al. 1988; Buijsman et al. 1987; Kucey 1988; Reynolds and Wolf 1988). The rate of ammonia emission from ground sources, such as freshly fertilized fields and cattle feedlots, is dependent on variables such as the pH, temperature, soil characteristics, rainfall, method of application, wind speed, etc. (Bouwmeester and Vlek 1981; Brunke et al. 1988; Denmead et al. 1982; Hoff et al. 1981; Kucey 1988; Nason et al. 1988; Reynolds and Wolf 1988). Ammonia can volatilize from sewage sludge that has been spread on the surface of the soil (Beauchamp et al. 1978; Ryan and Keeney 1975).

Biological activity in soil is believed to be the primary global source of atmospheric ammonia (Dawson 1977; Dawson and Farmer 1984). Crutzen (1983) suggested that the decay of organic material arising from dead plants and animals, etc., generates most of the atmospheric ammonia, while Galbally (1985) and Irwin and Williams (1988) suggested that animal excretions represent the dominant source of atmospheric ammonia.

Ammonia can be released to the atmosphere through the venting of gases during its production, storage, and transportation, and during its formulation or incorporation into secondary products (Buijsman et al. 1987). Long pipelines are used to transport ammonia from its site of manufacture to agricultural areas where it is used as fertilizer (Farm Chemicals Handbook 1987; LeBlanc et al. 1978). Releases to the atmosphere could occur at pumping stations and points of transfer along these pipelines, or from leaks. Large refrigerated tanks are used to store ammonia, and release to the environment can occur while venting the pressure in these tanks, or from leaks.

Ammonia can enter the atmosphere by volatilization from the wastewater of industrial processes which involve its production or use, and from the volatilization from the effluent of wastewater treatment plants (Roy and Poricha 1982; Wilkin and Flemal 1980). Ammonia has been found in the exhaust of automobile and diesel engines (Pierson and Brachaczek 1983). Release to the atmosphere can occur during the burning of coal (Bauer and Andren 1985). The latter process is thought to account for a significant proportion of the total anthropogenic ammonia released to the atmosphere (Crutzen 1983).

Natural sources of ammonia emissions to the atmosphere are volcanic eruptions, forest fires, and the microbial fixation of nitrogen (Galbally 1985; Hegg et al. 1987). Excreta from household pets, wild animals, and man himself are also contributing sources (Asman and Drukker 1988; Buijsman et al. 1987; Crutzen 1983).

5.2.2 Water

The major point source of release to surface waters is from the effluents of wastewater treatment plants (Wilkin and Flemal 1980). Ammonia can enter surface waters through the effluent of commercial processes in

5. POTENTIAL FOR HUMAN EXPOSURE

which ammonia is used or produced (Roy and Poricha 1982). Runoff from fertilized farmland and from areas of concentrated livestock production can also result in the transfer of ammonia to surface water (Wilkin and Flemal 1980). Surface water can absorb ammonia directly from the atmosphere near cattle feedlots, areas where the local atmospheric concentration may be high (Hutchinson and Viets 1969).

5.2.3 Soil

Ammonia can enter the soil by direct application of fertilizers. Of the total United States production of anhydrous ammonia, 27% is applied directly to the soil under pressure (CMR 1988). Approximately 80% of the United States production of ammonia is applied to soil in fertilizer formulations designed to release ammoniacal nitrogen. Application of natural fertilizers obtained from livestock excreta will also result in the release of ammonia to the soil (Beauchamp et al. 1982; Hoff et al. 1981). High levels of ammonia in soils can result from the decomposition of animal wastes on cattle feedlots or other confinement areas. Ammonia in soil can also arise from the decay of organic material from plants and animals, etc. (Dawson 1977; Dawson and Farmer 1984). Microbial fixation of nitrogen from the atmosphere is a natural and continual source of ammonia in soil (Galbally 1985).

In nature, there are many pathways for incorporation of ammonia into soil. Natural sources include microbial decomposition of dead plants and animals, and hydrolysis or breakdown of urea and nitrogenous waste products in animal excretions. Only a few species of microbiota can produce ammonia by the fixation of nitrogen; however, these species are widely dispersed throughout the soil (Crutzen 1983).

5.3 ENVIRONMENTAL FATE

In considering the environmental fate of ammonia, it is necessary to emphasize that ammonia is very important in nature and in nature's biological cycles. In our limited understanding of these cycles, ammonia can be considered a key intermediate. Nature has incorporated many mechanisms and rules for altering the distribution of ammonia through the biological system as circumstances dictate. An in-depth discussion of these phenomena is outside the scope of this document; however, it is important to understand that for ammonia, almost all organisms can contribute, either directly or indirectly, to the direction and distribution of the various environmental fate processes.

An important consideration that affects the transport and partitioning of ammonia in the environment is that ammonia is a base. As a base, the physical and chemical properties of ammonia are pH-dependent, and thus, environmental fate processes are also pH-dependent. For some environmental fate processes, a change in pH may only affect the relative rate of a process, while for others, it could change the direction or overall result

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of that process. The influence of pH on the environmental fate of ammonia will be discussed where appropriate. Temperature is also an important consideration in the environmental fate of ammonia. Temperature, although to a lesser extent than pH, affects the ammonia-ammonium equilibrium.

5.3.1 Transport and Partitioning

Atmospheric ammonia can be readily removed from the air by rain or snow washout (Adamowicz 1979; Kumar 1985). It can dissolve in clouds (Brimblecombe and Dawson 1984; Sprenger and Bachmann 1987) or fog (Johnson et al. 1987). Ammonia can be removed from the atmosphere through the direct absorption by surface waters in areas where the local atmospheric concentration is high (Hutchinson and Viets 1969). Uptake of atmospheric ammonia by different species of plants also occurs (Nason et al. 1988; Rogers and Aneja 1980). Depending on the local atmospheric concentration, however, plants can also release ammonia to the atmosphere (O'Deen and Porter 1986; Parton et al. 1988). It has been demonstrated by using $^{15}\text{NH}_3$ that minerals and dry soil can rapidly and effectively adsorb NH_3 from air containing trace quantities of this gas (Bremner 1965). Ammonia is the predominant basic gas in the atmosphere. As such, it is capable of rapidly reacting with gaseous H_2SO_4 , HNO_3 , or HCl , forming ammonium aerosols which can then undergo dry deposition (Irwin and Williams 1988).

If released to surface water, ammonia volatilizes to the atmosphere. The rate of volatilization of ammonia from water will increase with increasing pH and temperature, and can depend on other environmental factors as well. Gaseous or liquid ammonia added to water will increase the pH of the medium; the rate of volatilization may increase dramatically if large amounts are released to relatively small static bodies of water, such as rice paddies. Agitation will also increase the rate of volatilization. Georgii and Gravenhorst (1977) calculated the equilibrium concentration of ammonia above the Pacific Ocean. Using a constant concentration of 3 $\mu\text{mol/L}$, the ammonia concentration above the ocean as a result of increased volatilization changed from approximately 2.8-7 ppb as the pH increased from 8.0-8.4 (at 25°C). Volatilization of ammonia from flooded rice paddies was found to increase with increasing ammoniacal nitrogen concentration, pH, temperature, and wind velocity (Bouwmeester and Vlek 1981). Ammonia can also be taken up by aquatic plants as a source of nutrition.

Adsorption of ammonia to sediment and suspended organic material can be important under proper conditions. Adsorption to sediment should increase with increasing organic content, increased metal ion content, and decreasing pH. Ammonia, however, can be produced in, and subsequently released from sediment (Jones et al. 1982; Malcolm et al. 1986). The uptake of ammonia by fish can also occur under the proper conditions (Mitz and Giesy 1985). Acting as the final breakdown product for

5. POTENTIAL FOR HUMAN EXPOSURE

catfish, ammonia is normally released through the gills into the surrounding water, driven by a concentration gradient. If the water concentration is abnormally high, the direction of passive ammonia transport is reversed.

A complete discussion of the factors influencing the transport and partitioning of ammonia in soil is outside the scope of this document. Adsorption of ammonia occurs in most moist or dry soils, and ammonia is predominantly, but not exclusively, held as the ammonium ion. Generally, adsorption will increase with increasing organic content of the soil, and will decrease with increasing pH. Other factors that influence the adsorption of ammonia to soil are the presence of metallic ions, the microbial population, and its uptake by plants. The ammonia concentration, temperature, and wind speed can also subtly affect the adsorption process by influencing the rate of volatilization (Bouwmeester and Vlek 1981; Brunke et al. 1988; Denmead et al. 1982; Galbally 1985; Hoff et al. 1981; Kucey 1988; Nason et al. 1988; Reynolds and Wolf 1988). For example, ammonia loss from soil in a greenhouse experiment after the application of manure to the soil surface was found to be 14% of the applied ammonium at a soil pH=6.4 (manure pH=6.4). At a pH=7.0 (manure pH=7.8), 65% was lost by volatilization (Hoff et al. 1981). The threshold pH at which ammonia volatilization from soil was drastically reduced between pH 3.5 and 4.0 (Mahendrappa 1982).

Because ammonia, as ammonium ion, is the nutrient of choice for many plants (Rosswall 1981), uptake of soil ammonia by living plants is an important fate process. The rate of uptake by plants varies with the growing season. At normal environmental concentrations, ammonia does not have a very long lifetime in soil. It is either rapidly taken up by plants, bioconverted by the microbial population, or volatilized to the atmosphere. Because of these processes, ammonia does not leach readily through soil; thus, it is rarely found as a contaminant of groundwater. In soil, ammonia which results from the application of fertilizers is usually found in the top 10 inches of the soil (Beauchamp et al. 1982). However, nitrate derived from ammonia may penetrate groundwater.

5.3.2 Transformation and Degradation

5.3.2.1 Air

In air, a dominant fate process for ammonia is the reaction with acid air pollutants. The reaction of ammonia with HNO_3 and H_2SO_4 to form particulate ammonium (NH_4^+) compounds is rapid (Irwin and Williams 1988). The extent to which this process serves as a removal mechanism depends on the local concentrations of these acidic compounds. Thus (it is more important in areas of high industrial activity, and of lesser importance over rural areas. These ammonium compounds can then be removed by dry or wet deposition.

5. POTENTIAL FOR HUMAN EXPOSURE

The vapor-phase reaction of ammonia with photochemically produced hydroxyl radicals is known to occur. The rate constants for this reaction have been determined to be 1.6×10^{-13} cm³/molecule-set, which translates to a calculated half-life of 100 days at a hydroxyl radical concentration of 5×10^5 molecules/cm³ (Graedel 1978). This process reportedly contributes approximately 10% to the removal of atmospheric ammonia (Crutzen 1983). Since ammonia is very soluble in water, rain washout is expected to be a dominant fate process. The half-life for ammonia in the atmosphere was estimated to be a few days (Brimblecombe and Dawson 1984; Crutzen 1983; Dawson 1977; Galbally and Roy 1983; Moller and Schieferdecker 1985). The reaction of atmospheric ammonia with acidic substances in the air results in the formation of ammonium aerosols which can subsequently be removed from the atmosphere by dry or wet deposition.

5.3.2.2 Water

In surface water, groundwater, or sediment, ammonia can undergo sequential transformation by two processes in the nitrogen cycle, nitrification and denitrification, which would produce ionic nitrogen compounds, and from these, elemental nitrogen. The ionic nitrogen compounds formed from the aerobic process of nitrification, NO_2^- and NO_3^- , can then leach through the sediment or be taken up by aquatic plants or other organisms. High concentrations of nitrates in groundwater can cause methemoglobinemia in infants when contaminated water is ingested (Payne 1981). Elemental nitrogen formed from the anaerobic process of denitrification is lost by volatilization to the atmosphere.

In water, ammonia is in equilibrium with the ammonium ion, NH_4^+ . The ammonia-ammonium equilibrium is highly dependent on both the pH and, to a lesser extent, the temperature of the medium. In acidic waters, the equilibrium favors the ammonium ion.

5.3.2.3 Soil

In soil, ammonia can serve as a nutrient source, which can be taken up by plants and other organisms and be converted to organic-nitrogen compounds. Ammonia in soil can be rapidly transformed to nitrate by the microbial population through nitrification (Payne 1981). The nitrate thus formed will either leach through the soil or be taken up by plants or other organisms. Very high localized concentrations of ammonia could become toxic to plants, organisms, or the microbiota, thus decreasing the rate of the above biological processes, such that other fate processes dictated by the physical and chemical properties of ammonia can dominate until the ammonia concentration returns to a tolerable level. Specifically, ammonia may either be bound to soil or undergo volatilization to the atmosphere.

5. POTENTIAL FOR HUMAN EXPOSURE

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

In discussing the concentration of ammonia monitored in the environment, it is important to consider both ammonia and its conjugate acid, the ammonium ion. Independent determination of these compounds cannot always be achieved. In an analysis of the literature, it is difficult to separate aqueous ammonia concentration from aqueous ammonia-ammonium concentrations unless the investigators made a special effort to determine the amount of un-ionized ammonia. In this section of the document, ammonia will refer to the ammonia and ammonium concentration, and un-ionized ammonia will refer specifically to the ammonia concentration.

In the atmosphere, ammonia can exist in its gaseous state, dissolved in rain, fog, or clouds, or it can be found as ammonium in particulates and aerosols. These species can be analyzed for separately. For this reason, atmospheric ammonia concentrations reported in this document will refer to the concentration of gaseous ammonia, and not to the concentrations of ammonium compounds.

5.4.1 Air

Ammonia has a worldwide atmospheric background concentration. Estimates of the average global ammonia concentration are approximately 1-3 ppb (Crutzen 1983; Georgii and Gravenhorst 1977). Dawson and Farmer (1984) reported that the average value for the ammonia concentration in the southwestern United States to be 0.9 ppb, which may be considered a representative background value because at the site of these measurements, the prevalent winds came from the Pacific Ocean and there were no known urban or agricultural ammonia sources nearby. When atmospheric ammonia levels have been determined to be above background levels, the measurements can often be correlated with activity that might occur in nearby areas.

Based on early data on the concentration of ammonia in rain, Lau and Charlson (1977) determined a trend for the atmospheric ammonia concentration across the United States. The estimation of atmospheric ammonia content increased progressively starting from the east coast to the mid-west and on to the western states. Upon reaching the Pacific coast, the atmospheric ammonia concentration decreases. Although the values obtained in this study tend to be lower than those determined by more recent experiments, the conclusion appears valid, and is indicative of the trends found for the ammonia concentrations in the atmosphere. Atmospheric ammonia concentrations are expected to be highest near intense agricultural or livestock production areas, because of ammonia emissions from fertilizer and animal excreta, respectively. Lower concentrations are expected in the more industrialized areas because of diminished sources of agricultural emissions and the atmospheric reaction of ammonia with acidic compounds known to be produced in industrial emissions.

5. POTENTIAL FOR HUMAN EXPOSURE

Ground level ammonia concentrations taken at urban Hampton, and rural Langley, VA, ranged from 0.2-4.0 and 1.5-4.0 ppb, respectively, in the fall of 1979 (Harward et al. 1982). Ammonia concentrations obtained in December of 1979 on Long Island, NY, ranged from approximately 80-200 nmol/m³ (1.9-4.8 ppb) (Tanner 1982). The ground level ammonia concentrations in Claremont, Los Angeles, and Anaheim, CA, were less than 25 ppb (Russell et al. 1988). In Riverside and Rubidoux, CA, areas near dairy feedlots, the ground level ammonia concentrations were 37-132 ppb and approximately 10-100 ppb, respectively.

The ambient concentrations of ammonia determined at Whiteface Mt., NY, in 1982, ranged from approximately 0.3-5 ppb, with the hourly median and mean values both determined as 2.2 ppb (Kelly et al. 1984). Ammonia concentrations in rural Thurber, NV, ranged from approximately 0.5-2 ppb (Farmer and Dawson 1982). In the atmosphere over the world's oceans, ammonia concentrations ranged from approximately 0.28-5.6 ppb (Georgii and Gravenhorst 1977).

Several investigators have studied the seasonal variation of ammonia concentrations in the atmosphere. In Hampton, VA, the ground level ammonia concentrations during the spring and summer were 10 and 1 ppb, respectively (Levine et al. 1980). The difference in concentration may have been due to volatilization of ammonia resulting from springtime application of fertilizer in nearby agricultural areas. In Warren, MI, the average ammonia concentrations measured during the summer, fall, winter, and spring were 0.85, 0.37, 0.10, and 0.16 ppb, respectively. The difference in concentrations was attributed to fluctuations in emissions from livestock excreta, where activity in summer is greater than in winter (Cadle 1985). Additionally, in colder weather, microbial activity would be expected to decrease, and thus ammonia emissions from the decay of organic matter would also be expected to decrease. Ammonia emissions from animal excretions also fluctuate with the time of day (Beauchamp et al. 1982; Brunke et al. 1988).

The concentration of ammonia in the atmosphere decreases with altitude. Levine et al. (1980) found that an ammonia concentration of 10 ppb measured at ground level decreased to a concentration of 1.5-3 ppb at a height of 10 km. In a historical modeling study on the European production of ammonia, levels based on ammonia release from livestock (dominant), fertilizer production and application, human and domestic animals, and sewage sludge resulted in average atmospheric ammonia concentrations ranging from 0.6-1.4 ppb for 1970 and 0.7-5.6 ppb for 1980. The greatest increase occurred between 1950 and 1980, when synthetic fertilizer application and high nitrogen content feed grains were widely used (Asman and Drukker 1988). The ammonia concentration over a field during the application of gaseous ammonia fertilizer was as high as 213 pg/m³ (300 ppb) (Denmead et al. 1982). Over cattle feedlots, atmospheric ammonia concentrations have been measured at 373-1540 pg/m³ (520-2160 ppb) (Hutchinson et al. 1982).

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5.4.2 Water

The concentration of ammonia in the Ochlocknee River at the head of Ochlocknee Bay, FL, ranged from 1.8-2.5 μM (approximately 31-43 ppb), and a concentration of 0.5-1.5 μM (approximately 8.5-26 ppb) was determined at the mouth of the bay (Seitzinger 1987). The concentration determined in the Ochlocknee River is consistent with levels reported for unpolluted tropical rivers (Meybeck 1982). Typical ammonia levels in the Skunk Creek, IA, upstream from a municipal sewage treatment facility were below 1 mg/L (1000 ppb) (Crumpton and Isenhardt 1988). Downstream of the facility, ammonia levels peaked at approximately 16 mg/L (16,000 ppb), with levels of un-ionized ammonia ranging <1-2.2 mg/L (<1000-2200 ppb). The levels of undissociated ammonia were directly related to pH fluctuations in the river. The author did not discuss why the upstream concentration was so high. The mean ammonia concentration in three Illinois rivers ranged from 0.28 mg/L (280 ppb) to 6.08 mg/L (6880 ppb). The lower values were associated with agricultural sampling points and the higher values were associated with urban sampling points (Wilkin and Flemal 1980).

The ammonia concentration measured in Hamilton Harbour, Ontario, was typically 0.1-3 mg/L (100-3000 ppb). This body of water is used for water transport, as a source for industrial cooling water, and a receptor for wastewater disposal (Snodgrass and Ng 1985).

No representative data regarding the concentration of ammonia in groundwater were located. Low levels of ammonia have been found in groundwater wells under cattle and poultry feed lots, and in shallow wells. Wells 3-6 m deep showed little variation in ammonia concentration over a 3-year period where varying amounts of chicken manure were spread over agricultural plots, except when excessive amounts (54-179 mton/ha) were applied (Liebhardt et al. 1979). Shallow wells in North Carolina had typical ammonia concentrations of 0.1-1 ppm (100-1000 ppb), which were independent of land use, plant type, and amount of fertilization (Gilliam et al. 1974). Water samples from wells on four schoolyards in Michigan which used septic tank sewage systems had ammonia concentrations ranging from 0-733 ppb (Rajagopal 1978). In the Netherlands, the ammonium concentration detected in sample cups buried 1.2 m in the ground ranged from 0-2.3 mg/L (0-2300 ppb) (Krajenbrink et al. 1988). Ammonia was not found in deep wells analyzed in this study. The high adsorptivity of ammonium to soil and the rapid conversion of ammonia to nitrate by microbial action are both consistent with the usual finding of very low ammonia concentrations in groundwater.

Ammonia was measured in rain and snow samples from three sites in northern Michigan in 1978-79. Concentrations ranged from 1.4-205 $\mu\text{eq/L}$ (23.8-3500 ppb), with mean values for each site of 47.9, 33.6, and 37.1 $\mu\text{eq/L}$ (816, 572, and 632 ppb). Concentrations were generally greatest in the spring and fall, and were lowest during the winter (Munger 1982). Ammonia concentrations in bulk precipitation obtained in the Netherlands had

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median values ranging from 78 $\mu\text{mol/L}$ (1330 ppb) in ocean areas to 299 $\mu\text{mol/L}$ (5090 ppb) in heavily agricultural areas (Schuurkes et al. 1988).

Ammonia concentration in the influent to sewage treatment plants and thus the effluent from sewer systems can typically range from 10,000-20,000 ppb (Englande et al. 1978; Hauser 1984; Martel et al. 1980). Wastewater treatment plant effluent is one of the few types of point sources of ammonia emissions to surface water. In a study of these plants, eight of nine plants exceeded the guideline ammonia concentration (0.5 mg/L), with measured median values at these sites ranging from 0.08-15 mg/L (80-15,000 ppb) (Englande et al. 1978).

Ammonia has been found in water samples from 18 of 357 hazardous waste sites in the contract laboratory program statistical database at mean and median concentration ranges of 1-14,025 and 1-16,157 ppb, respectively (Viar 1987).

No data were located in the available literature regarding ammonia concentrations in drinking water. This may be attributed to the facile reaction between ammonia (and ammonium) and the chlorinating agents used in water treatment plants (Morris 1978).

5.4.3 Soil

A 4-year study on ammonia levels in the soil (0-10 cm deep) of an open field (samples obtained in early May) ranged from 1-5 $\mu\text{g/g}$ (1000-5000 ppb) (Beauchamp et al. 1982). The day after application of liquid cow manure, the soil concentration ranged from 2-3349 $\mu\text{g/g}$ (2000-3,349,000 ppb). Five days after application, the concentration of ammonium ranged from 2-848 $\mu\text{g/g}$ (2000-848,000 ppb). The greatest ammonia concentration was in the uppermost 4 cm of soil.

Ammonia was found at 15 of 1177 hazardous waste sites on the National Priority List (NPL) of highest priority sites for possible remedial action (VIEW 1989). The reported frequency of ammonia in soil samples was 22 of 357 hazardous waste sites in the contract laboratory program statistical database, with mean and median concentrations in the range 1250-1,879,000 and 1500-1,879,000 ppb, respectively (Viar 1987).

5.4.4 Other Media

The ammonia concentrations measured in the plumes of seven forest fires in the Western United States ranged from 7-130 ppb; the median value of the 13 measurements was 37 ppb (Hegg et al. 1987,1988). Ammonia has been found in the exhaust of automobile and diesel engines (Pierson and Brachaczek 1983). Ammonia has also been determined to be a component of tobacco and cigarette smoke (Sloan and Morie 1974).

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5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The most probable routes by which the general population is exposed are by the inhalation of ammonia that has volatilized from common household cleaning products and through dermal contact during the use of these products. Inhalation exposure to ammonia by some members of the rural population may occur for those who are near agricultural areas during the fertilizer application period and those near animal feedlots or confinement areas, and those who apply anhydrous ammonia to fields.

In the NOHS Survey of 1972-1974, it was statistically estimated that 2,524,678 workers are exposed to ammonia in the United States (RTECS 1988). According to the NOES Survey 1981-1984, 569,950 workers were estimated to be exposed (NIOSH 1988). A correlation of data from the EPA Air Toxics Emission Inventory with industrial source codes (SIC codes) shows that volatile emissions of ammonia are associated with 212 different industrial classifications (Pacific Environmental Services, Inc. 1987).

Workers in swine and poultry confinement buildings may be exposed to elevated levels of ammonia (Attwood et al. 1987; Donham and Popendorf 1985; Jones et al. 1984; Leonard et al. 1984). Average ammonia concentrations in the air of these buildings depend on numerous factors; representative values ranged from 0.28-42.2 ppm (280-42,200 ppb) (Attwood et al. 1987).

Ammonia air levels at an ammonium phosphate fertilizer production plant ranged from 3-75 ppm (3000-75,000 ppb) (Apol and Singal 1987). In a Finnish plywood factory, short-term ammonia concentrations during the mixing of urea-formaldehyde glue were 50-70 ppm (50,000-70,000 ppb) (Kauppinen 1986). Ammonia concentrations at 42 facilities using a blue-line printing system were 1-40 ppm (1000-40,000 ppb) (Tuskes et al. 1988). Workers at coal gasification units may be exposed occupationally to ammonia (Van Hoesen et al. 1984). Workers at ammonia transportation and storage facilities can be exposed to ammonia during the transfer between facilities, the venting of built-up pressure in tanks, and during leaks or spills.

Farmers can be exposed to ammonia when applying fertilizer. The ammonia concentration over a field during the application of gaseous anhydrous ammonia fertilizer was as high as 213 $\mu\text{g}/\text{m}^3$ (300 ppb) (Denmead et al. 1982). Workers at cattle production facilities and those who work under conditions where volatilization from animal excreta would be enhanced, may be occupationally exposed to ammonia. Over cattle feedlots, atmospheric ammonia concentrations have been measured at 373-1540 $\mu\text{g}/\text{m}^3$ (520-2160 ppb) (Hutchinson et al. 1982). Exposure to ammonia can occur by inhalation in the liquid manure storage facilities of swine confinement buildings. Ambient air levels have been measured at up to 50 ppm (50,000 ppb) in these facilities (Donham et al. 1982).

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5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURE

Workers in industries that commonly use ammonia, especially if there are no adequate safety and/or venting systems, may be at risk for potentially high exposure to ammonia. The general population is at risk to high levels of exposure if cleaning products containing concentrated solutions of ammonia are used in small, enclosed, or unventilated rooms.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ammonia is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ammonia.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of ammonia have all been well documented, and there do not appear to be any data needs in this area.

Production, Use, Release, and Disposal. The large amounts of ammonia produced in nature and in household products indicate that the risk for human exposure to ammonia exists. Data regarding the commercial production, disposal, and use of ammonia are well understood. Data regarding the production of ammonia by natural organisms, and its global and regional concentrations are not as well understood. This information would be useful in determining the contribution of anthropogenic ammonia to the global budget of this compound, which would help in determining man's influence on the global cycle.

According to the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, 9313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

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Environmental Fate. Since ammonia is a key intermediate in the nitrogen cycle, the environmental fate of ammonia should be interpreted in terms of its involvement in this cycle. Information available on the environmental fate of ammonia is sufficient to define the basic trends, and sufficient data are available regarding the direction of changes in these trends resulting from changes in the key variables. There are many subtle facets of the fate of ammonia in the environment which depend on nature and its cycles. Thus, accurately predicting the environmental fate of ammonia is not possible with our present knowledge.

An understanding of the environmental fate of ammonia is important when considering that man's contribution to the global ammonia budget is predicted to grow over the years. A complete understanding of the environmental fate of ammonia will then allow an understanding of any changes that might occur from the role of ammonia in the nitrogen cycle. Since all living organisms depend on the nitrogen cycle, either directly or indirectly, this information would allow any decisions concerning ammonia to be made in an informed and prudent manner.

Bioavailability from Environmental Media. The bioavailability of ammonia from air and water has been examined rather extensively in animals. Bioavailability from soil has not been studied, although it is not a likely source of exposure.

Food Chain Bioaccumulation. Ammonia is a naturally-occurring compound, a key intermediate in the nitrogen cycle. Since it is continually recycled in the environment, bioaccumulation, as it is usually considered, does not occur. Thus, data on this process are not warranted.

Exposure Levels in Environmental Media. As an intermediate in the nitrogen cycle, ammonia is naturally present in environmental media. Measurements of ammonia in environmental media are sufficient to distinguish between background concentrations and elevated concentrations. Data regarding ammonia levels in soil samples, however, appear not to be as complete as the database for air and water.

Determining low level concentrations of atmospheric ammonia in the presence of ammonium salts is difficult. Recently, investigators have been establishing new methods for the analysis of ammonia in the presence of ammonium compounds (see Chapter 6, Analytical Methods). If highly accurate values for low levels of ammonia are necessary, then a re-evaluation of older literature values might be necessary.

Exposure Levels in Humans. Data regarding the exposure levels of ammonia are sufficient for understanding the sources and approximate magnitudes of human exposure. Quantitative monitoring data for specific circumstances, occupations, or events, as reported in the current literature, might be considered to be lacking. Also lacking are monitoring data for ammonia concentrations in the average household, as recent studies

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suggest that indoor concentrations of chemical compounds might be greater than those outside the home.

Exposure Registries. No exposure registries for ammonia were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this compound.

5.7.2 On-going Studies

No on-going studies on ammonia in the environment were identified. Remedial investigations and feasibility studies conducted at the NPL sites known to be contaminated with ammonia could add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries, and may increase knowledge regarding the fate of ammonia in the environment. No other long-term research studies pertaining to the environmental fate of ammonia or **to** occupational or general population exposures to ammonia were identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring ammonia in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify ammonia. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect ammonia in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

The determination of ammonia (as dissolved NH_3 and ammonium ion) in blood, plasma, or serum is reportedly of value in detecting existing or impending hepatic coma and Reyes Syndrome (Meyerhoff and Robins 1980; Tietz 1970). The determination of ammonia in urine had been used as an indicator of the kidney's ability to produce ammonia; however, this procedure has been replaced by more modern and accurate tests for kidney function. Procedures for the determination of ammonia in these samples are found in Table 6-1. Ammonia is also tested for in calculi (Tietz 1970); however, this is not a quantitative test and is not included in Table 6-1.

The ammonia content of freshly drawn blood rises rapidly on standing because of the deamination of labile amides such as glutamine (Henry 1964). At room temperature, the ammonia content can increase by a factor of two or three' in several hours. Therefore, it is important to keep the specimen cold and perform the analysis as soon as possible. Alternatively, the sample should be frozen. The ammonia content of iced samples remains constant for 20 minutes; the ammonia content of frozen (-20°C) samples remains constant for several days (Tietz 1970). Positive errors in ammonia levels may result from ammonia contamination of reagents or pick-up of ammonia from the atmosphere. In addition, bacterial action can lead to erroneously high values due to the hydrolysis of urea. This reaction is the chief cause for the formation of ammonia in unacidified urine on standing (Henry 1964).

Traditionally, Kjeldahl distillation methods have been used to determine ammonia levels in biological tissue. The determination of ammonia levels has been considered as a method of ascertaining the microbial quality of meat (Parris 1984). In these procedures, ammonium is converted to ammonia which is subsequently trapped in acid and analyzed titrimetrically or calorimetrically. High values sometimes result because of the cleavage

TABLE 6-1. Analytical Methods for Determining Ammonia in Biological Materials

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Urine	24-hr specimen, add HCl, refrigerate.	Colorimetric (Berthelot reaction)	NR	NR	Teitz 1970
Serum, plasma, whole blood	Freeze at -30°C or ice and analyze immediately.	Membrane based ammonia-selective electrode	NR	-7.0-14% error, 102% average recovery	Meyerhoff and Robins 1980

NR = not reported

6. ANALYTICAL METHODS

of protein amino groups and also the formation of ammonia by deamination reactions (Parris and Foglia 1983). Other techniques use the ammonia-selective electrode and enzymatic assays. Discrepancies have been reported between results using electrodes and those using more specific enzymatic procedures because the ammonia electrode responds to both ammonia and volatile amines (Parris and Foglia 1983). Chromatographic separation of ammonia and volatile amines after derivatization have also been used to obtain specificity (Parris 1984).

6.2 ENVIRONMENTAL SAMPLES

Water and wastewater samples can be analyzed for ammonia by EPA Test Methods 350.1, 350.2, and 350.3 (EPA 1983). Analogous procedures, methods 417B, 417D, 417F, and 417G, have been approved and published jointly by the American Public Health Association, American Water Works Association, and Water Pollution Control Association (Greenberg et al. 1985). These methods are suitable for drinking, surface, and saline waters, and domestic and industrial effluent. These and other methods for determining ammonia in environmental samples are listed in Table 6-2, Ammonia is reported as ammonia nitrogen. Two methods that are suitable for water employ calorimetric techniques, nesslerization, and phenate methods. Nessler's reagent, an alkaline mixture of mercuric and potassium iodide, produces a yellow to brown color with ammonia, whereas the phenate reagent, alkaline phenol, and hypochlorite produce a blue color (EPA 1983, Greenberg et al. 1985). In the titrametric method, the distillate is titrated with standard sulfuric acid with an appropriate indicator. The ammonia electrode employs a hydrophobic gas-permeable membrane to separate the sample solution from an internal ammonium chloride solution, Ammonia diffusing through the membrane changes the pH of the internal solution and is sensed by a pH electrode. For determining $\text{NH}_3\text{-N}$ concentrations above 5 mg/L, the titrametric and ammonia-selective electrode methods are to be preferred. Methods for determining ammonia in water and soil measure ammoniacal nitrogen, the sum of NH_3 and NH_4^+ . In the determination of ammoniacal nitrogen in soil, exchangeable ammonium should be distinguished from nonexchangeable ammonium. The former is usually defined as that which can be extracted with KCl (or K_2SO_4) at room temperature (Bremner 1965). Nonexchangeable ammonium is fixed nitrogen. In the determination of nonexchangeable ammonium, organic ammonium is first removed and then the minerals containing the nonexchangeable ammonium are decomposed with HF and the NH_4^+ released. In calorimetric procedures, turbidity and sample color may lead to interference. To eliminate interference, the pH of the sample may be raised and the ammonia distilled. Care should be taken to prevent losses in water samples due to volatilization and microbial transformation. To prevent such losses, samples should be acidified soon after collection and refrigerated. Care should also be taken during storage and treatment of soil samples to prevent ammonia loss or gain. It has been demonstrated that dry soil can rapidly adsorb trace amounts of ammonia from the atmosphere and that extensive amounts of ammonia can be lost during air drying (Bremner 1965). Additionally, in samples containing both ammonium and nitrite,

TABLE 6-2. Analytical Methods for Determining Ammonia in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Air	Passive collection using 0.01 N H_2SO_4 in liquid sorbent badge.	Method 6701, ion chromatograph, conductivity detection	1 μg NH_3 /sample	No bias between 6.9 and 48 ppm; +19% at 148 ppm	Apol and Singal 1987
	Collection on H_2SO_4 -coated activated carbon beads in sampling tube	Ion chromatography	2 μg NH_3 /sample	95-110% recovery	Bishop et al. 1986
	Known volume of air drawn through prefilter and H_2SO_4 -treated silica gel	NIOSH S347, ammonia-specific electrode	NR	97.6% mean recovery	SRI 1988
Water	None	Method 350.1 colorimetric, automated phenate	0.01 mg/L	107% and 99% recoveries at 0.16 and 1.44 mg NH_3 -N/L, respectively	EPA 1983
	Removal of residual chlorine with sodium thiosulfate, distillation	Method 350.2 Nessler reagent, colorimetric, titrametric; or ammonia specific electrode	0.05 mg N/L for colorimetric and potentiometric 1.0 mg N/L for titrametric	28.12 to -0.46R bias between 0.21 and 1.92 mg N/L	EPA 1983
	None	Method 350.3 ion selective electrode	0.03 mg N/L	96 and 91% recoveries at 0.19 and 0.13 mg N/L, respectively	EPA 1983
Soil, exchangeable ammonium	Extract soil with 2N KCl	Method 84-3, steam distillation with MgO , titration	NR	NR	Bremner 1965
Soil, nonexchangeable (fixed) ammonium	Pretreat soil with $KOBr$ - KOH , shake with 5 N HF -1N HCl for 24 hours	Method 84-7, steam distillation with KOH , titration	NR	NR	Bremner 1965

NR = not reported

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losses during air drying may occur due to the reaction between these ions and the resulting formation and release of nitrogen gas (Bremner 1965).

The detection limit of analytical methods for determining ammonia in air depends on the amount of air collected in a liquid or solid adsorbent. Sampling is performed with passive samplers or by drawing a volume of air through the adsorbent using a pump. Particulate contaminants such as ammonium salts may be removed by a prefilter. For ambient determinations, larger volumes of air must be sampled than those appropriate for occupational determinations where ammonia levels are higher. Recent methodological developments permit continuous monitoring of atmospheric ammonia down to 0.1 ppb (Pranitis and Meyerhoff 1987). This method employs a specially designed flow-through, ammonia-selective electrode with a sniffer tube. Ammonia may be present in air in both the vapor and particulate phase as ammonia gas and as ammonium salts. While analytical methods may distinguish between these phases, most standard methods do not. In the methods in Table 6-2, the sample is collected in sulfuric acid and un-ionized ammonia will be converted to the ionic form. Methods have been developed that determine gaseous ammonia alone or gaseous and particulate forms of ammoniacal nitrogen separately. These methods use filter packs or sampling tubes coated with a selective adsorbent (denuder tube) to separate the phases (Dimmock and Marshall 1986; Knapp et al. 1986; Rapsomanikis et al. 1988). In these methods, gaseous ammonia is trapped by an adsorbent (e.g., oxalic acid, phosphoric acid) on a coated filter or denuder tube. In filter methods, errors may arise due to ammonia interactions occurring on the filter and volatilization of retained ammonium salt (Dimmock and Marshall 1986; Rapsomanikis et al. 1988). There is evidence that ammonium nitrate in particulate matter is in equilibrium with ammonia, which would contribute to small positive errors for ammonia and small negative errors for ammonium (Doyle et al. 1979).

Many analytical methods may be used for the determination of levels of ammonia. A discussion of these methods is beyond the scope of this document. For a review of new developments in the methodology for determining ammonia in water and air, see MacCarthy et al. (1987) and FOX (1987), respectively.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ammonia is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ammonia.

6. ANALYTICAL METHODS

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Biomarkers of Exposure and Effect. No unique biomarkers for exposure or effects exist for ammonia. Until one has been determined, methodology for the determination of biomarkers must be preceded by an experimental identification of a unique biomarker of human exposure OK effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining ammoniacal nitrogen in environmental media are well developed and adequate. Standardized methods are available from EPA, NIOSH, and other sources. Analytical methods are also well developed for oxidation products of ammonia. Since there are multiple sources of these compounds in the environment, their analysis is not generally used to study the disappearance of ammonia.

6.3.2 On-going Studies

No on-going studies regarding new analytical methods for measuring ammonia in biological materials or environmental media were located in the literature.

7. REGULATIONS AND ADVISORIES

International guidelines for ammonia were not located. National and state regulations and guidelines pertinent to human exposure to ammonia are summarized in Table 7-1.

Ammonia is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: fertilizer manufacturing, petroleum refining, iron and steel manufacturing, ferroalloy, glass manufacturing, asbestos, timber products processing, meat products processing, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black, and nonferrous metal forming (EPA 1988a).

The U.S. FDA (1973) determined that concentrations of ammonia and ammonium compounds normally present in food do not suggest a health risk; ammonia and ammonium ions are recognized to be integral components of normal metabolic processes. However, some restrictions have been placed on levels of ammonium salts allowable in processing of foods. Maximum allowable levels in processed foods are as follows: 0.04-3.2% ammonium bicarbonate in baked goods, grain, snack, foods and reconstituted vegetables; 2.0% ammonium carbonate in baked goods, gelatins and puddings; 0.001% ammonium chloride in baked goods and 0.8% in condiments and relishes; 0.6-0.8% ammonium hydroxide in baked goods, cheeses, gelatins and puddings; 0.01% monobasic ammonium phosphate in baked goods; 1.1% dibasic ammonium phosphate in baked goods, 0.003% in nonalcoholic beverages and 0.012% for condiments and relishes.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Ammonia

Agency	Description	Value	Reference
<u>National</u>			
Regulations:			
a. Air:			
OSHA	PEL	50 ppm	OSHA 1985 19 CFR 1910.1000
b. Nonspecific media:			
EPA OERR	Reportable quantity		EPA 1985
	Ammonia	100 lb	50 FR 13456
	Ammonia salts:		(4/4/85)
	ammonium acetate	5000 lb	40 CFR 117 and 302
	ammonium benzoate	5000 lb	
	ammonium bicarbonate	5000 lb	
	ammonium bichromate	5000 lb	
	ammonium bifluoride	5000 lb	
	ammonium bisulfite	5000 lb	
	ammonium carbamate	5000 lb	
	ammonium carbonate	5000 lb	
	ammonium chloride	5000 lb	
	ammonium chromate	1000 lb	
	ammonium citrate, bibasic	5000 lb	
	ammonium fluoborate	5000 lb	
	ammonium fluoride	5000 lb	
	ammonium hydroxide	1000 lb	
	ammonium oxalate	5000 lb	
	ammonium picrate	1 lb	
	ammonium silicofluoride	1000 lb	
	ammonium sulfamate	5000 lb	
	ammonium sulfide	5000 lb	
	ammonium tartrate	5000 lb	
	ammonium thiocyanate	5000 lb	
	ammonium thiosulfate	5000 lb	
	ammonium vanadate	1 lb	
Guidelines			
a. Air:			
ACGIH	TLV/TWA	25 ppm	ACGIH 1988
	STEL	35 ppm	ACGIH 1988
NIOSH	Recommended exposure limit		
	5-min ceiling	50 ppm	NIOSH 1985
<u>State</u>			
a. Air:			
	Acceptable ambient air concentration		NATICH 1988
Connecticut	Ammonia (7664-41-7)	360 $\mu\text{g}/\text{m}^3$	8-hr average
Florida-Tampa		0.36 mg/m^3	8-hr average
Kansas		42.857 $\mu\text{g}/\text{m}^3$	annual average
Kansas-Kansas City		42.857 $\mu\text{g}/\text{m}^3$	1-yr average
Massachusetts		24.0 $\mu\text{g}/\text{m}^3$	24-hr average
North Carolina		2.70 mg/m^3	15-min average
North Dakota		0.18 mg/m^3	8-hr average
North Dakota		0.27 mg/m^3	1-hr average
Nevada		0.429 mg/m^3	8-hr average
New York		360 $\mu\text{g}/\text{m}^3$	1-yr average
South Dakota		360 $\mu\text{g}/\text{m}^3$	8-hr average
Virginia		250 $\mu\text{g}/\text{m}^3$	24-hr average
Wyoming		429 $\mu\text{g}/\text{m}^3$	1-hr average

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Value	Reference
New York	Ammonium bromide (12124-97-9)	30 $\mu\text{g}/\text{m}^3$ 1-yr average	
Connecticut	Ammonium chloride fume (12125-02-9)	200 $\mu\text{g}/\text{m}^3$ 8-hr average	
North Dakota		0.10 mg/m^3 8-hr average	
North Dakota		0.20 mg/m^3 1-hr average	
Nevada		0.238 mg/m^3 8-hr average	
South Carolina		250 $\mu\text{g}/\text{m}^3$ 24-hr average	
South Dakota		200 $\mu\text{g}/\text{m}^3$ 8-hr average	
Virginia		150 $\mu\text{g}/\text{m}^3$ 24-hr average	
Connecticut	Ammonium sulfamate (7773-06-0)	200 $\mu\text{g}/\text{m}^3$ 8-hr average	
North Dakota		0.1 mg/m^3 8-hr average	
Nevada		0.238 mg/m^3 8-hr average	
Virginia		150 $\mu\text{g}/\text{m}^3$ 24-hr average	

^aReference dose for chronic oral exposure applies to ammonium sulfamate.

ACGIH = American Conference of Governmental Industrial Hygienists

EPA = Environmental Protection Agency

NIOSH = National Institute for Occupational Safety and Health.

OERR = Office of Emergency and Remedial Response

OSHA = Occupational Safety and Health Administration

PEL = Permissible Exposure Limit

TLV = Threshold Limit Value

TWA = Time-Weighted Average

STEL = Short-Term Exposure Limit

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the toxicological profiles.

Adsorption Coefficient (Koc) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

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Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose₍₅₀₎ (LT₅₀) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

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Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (Kow) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

ql* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX: PEER REVIEW

A peer review panel was assembled for ammonia. The panel consisted of the following members: Dr. Joseph Borowitz, Department of Pharmacology and Toxicology, Purdue University; Dr. Robert Wilson, Department of Biochemistry and Molecular Biology, Mississippi State University; and Dr. Donald Morgan, Private Consultant. These experts collectively have knowledge of ammonia's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.